FORMULATION AND EVALUATION OF BILAYER MATRIX TABLET OF ANTI HYPERTENSIVE DRUG

A dissertation submitted to

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

CHENNAI- 600 032.

In partial fulfillment of the requirements for the award of Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted
By

Reg No:261211155

DEPARTMENT OF PHARMACEUTICS

EDAYATHANGUDY.G.S PILLAY COLLEGE OF PHARMACY

NAGAPATTINAM-611002

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Under the guidance of

Prof.Dr.M.Murugan, M.Pharm.,Ph.D.,

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CERTIFICATE

This is to certify that the dissertation entitled "FORMULATION AND EVALUATION OF BI LAYER MATRIX TABLET OF ANTI HYPERTENSIVE DRUG" submitted by **KACHARLA ANJAIAH** (Reg No:261211155) in partial fulfillment for the award of degree of Master of Pharmacy to the Tamilnadu Dr. M.G.R Medical University, Chennai is an independent bonafide work of the candidate carried out under my guidance in the Department of Pharmaceutics, Edayathangudy.G.S.Pillay College of Pharmacy during the academic year 2013-2014.

Place: Nagapattinam

Date:

Prof.Dr.M.Murugan, M.Pharm.,Ph.D.,

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1

INTRODUCTION

1. INTRODUCTION

Cardiovascular diseases account for a large proportion of all deaths and disability worldwide. Global Burden of Disease (GBD) Study reported that there were 5.2 million deaths from cardiovascular diseases in economically developed countries and 9.1 million deaths from the same causes in developing countries . Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals, and approximately 7.1 million deaths per year may be attributable to hypertension [44]. Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. Pooling of Indian epidemiological studies shows that hypertension is present in 25% urban and 10% rural subjects. Therefore cost effective approaches to optimally control blood pressure among Indians are very much needed. Although novel drug-delivery systems have been used in other areas of medicine, their application in the treatment of hypertension has been relatively recent[1].

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explode for systematic delivery of drug via various pharmaceutical products of different dosage form. Popularity of oral route may be ease of administration as well as traditional belief that by oral administration the drug is well adsorbed as food stuff ingested daily[2].

In recent times, various developed and developing countries move towards combination therapy for treatment of multiple diseases and disorders requiring long term therapy such as hypertension and diabetes. Combination therapy have various advantages over monotherapy such as problem of dose dependent side effects is minimized, a low dose combination of two different agents reduces the dose related risk, the addition of one agent may potentiate effects of other agent.

Using low dosage of two different agents minimizes the clinical and metabolic side effects that occur with maximal dosage of individual component of the combined tablet and thus dose of the single components can be reduced. Bilayer tablets are novel drug delivery systems where combination of two or more drugs in a single unit having different release profiles improves patient compliance, prolongs the drugs action, avoid saw tooth kinetics resulting in effective therapy along with better control of plasma drug level.

Bilayer tablet are very common dosage form for drugs such as captopril, metoprolol, amoxicillin and potassium clavuanate, propranolol hydrochloride, bambuterol hydrochloride. Joint National Committee VI recognized the value of combination therapy and suggested that combining drug with different modes of action will often allow smaller doses of drugs to be used to achieve control and minimize the potential dose dependent side effects.

JNC VI recommended that the combination of a low dose of two drugs in fixed dose combination is an appropriate choice for initial treatment of any chronic disease. Hence management of multiple diseases can be effectively and better done by bilayer tablet or layering in tablet.

Layered tablet[3,4]:

Layer tablet are composed of two or three layers of granulation compressed together. They have appearance like as sandwich because the edges of each layer are exposed. This dosage form has the advantage of separating two incompatible substances with an inert barrier between them. Layer tablet may be bilayer, trilayer or multilayer depending upon the number of layer.

Multilayer tablets:

This tablet consists of two or more layers of materials compressed successively in the same tablets. The colour of each layer may be the same or different. The tablets having layers of different colour are known multicoloured tablets.

Multilayer tablets are tablets made by compressing several different granulations fed into a die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for two or three layer. More are possible but the design becomes very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes.

Advantage of multilayer tablets:

- This dosage form has the advantage of separating two incompatible substances with an inert barrier between them
- It makes possible sustained-release preparations with the immediate-release quantity in one layer and the slow release proportion in the second. A third layer, with an immediate release might be added.
- The weight of each layer can be accurately controlled, in contrast to putting one drug of a combination product in a sugar coating.
- Two-layer tablets require fewer materials than compression coated tablets,weigh less, and may be thinner.
- Monograms and other distinctive markings may be impressed in the surface of the multilayer tablets.
- Colouring the separate layer provides many possibilities for unique tablet identity.
- Analytical work may be simplified by the separation of layer prior to assay.
- Since there is no transfer to a second set of punches and dies, as with the dry coating machine, odd shapes (such as triangle, squares, and ovals) present no operating problems except for those common to keyed tooling.

Problems in layered tablets:

- Lack of proper bonding of two layers
- Stress due to high compression force degrades certain actives e.g ramipril.

Bilayer tablets:

- Pharmaceutical tablet manufacturers have long sought to define and optimize the process utilized for producing double-layer tables. Whether driven by capacity requirements, marketing-based ideas or simple physics, there are always unique factors to be considered when developing a standard procedure for a repeatable manufacturing process. The creation of one solid dosage form, in particular, has long been thought of as a process that could be more accurately described as an art form.
- Double- layer (or bi-layer) tablets have been around for recentime. Quitepossibly the earliest uses of this dosage form were driven form a marketing perspective, with emphasis placed on the perception of the consumer who would be utilizing the product. A tablet with two mutually exclusive ―layers represented by two clearly different colours, provided manufacturers with a way to produce a product that looked more interesting than a standard white ―pill. While

this motivation still has its place in modern pharmaceutical manufacturing the double-layer dosage form has evolved into much more than a product with purely visual appeal. Some double-layer products are ultimately coated, anyway, with the final form appearing to be comprised of one uniform substance.

Potential Reason for Considering the Double-layer Dosage Form:

One of the more common reasons that have developed for wishing to manufacture double-layer product centers on sustained release versus immediate release active ingredients and the related bioavailability of each within the human body. It is the intention of the manufacturer in some cases to formulate products that utilize two different actives, one whose pharmacological effect is available to the body shortly after it is ingested (immediate release) and another that fulfills its role more slowly over a longer period of time (sustained release). These two functions can be neatly delivered in the same tablet by separating the actives into two distinct layers.

Some active ingredient combinations for a tablet may also be better suited to the double-layer form if they cannot easily be blended into the same final formulation. Certain ingredient may simply need to be physically separated due to incompatibility. An example of a characteristic that might foster such incompatibility would be disparate dissolution rates.

- Another modern catalyst for utilization of the double-layer form focuses on the idea of product line extension. As patent protection begins to wane manufactures can sometimes breathe a new life into a product line by modifying its format or presentation. This can in some cases be achieved by creating a double-layer version of what was historically in mono-layer tablet. The best cases may result in a new patent for the

revised form, thereby extending the life of a product line.

- Perhaps the most interesting emerging use for a double-layer tablet focuses on the desire to thwart abuse of a constituent ingredient. Abusers of pharmaceutical preparation have been increasingly successful and inventive in their ability to extract powerful ingredient for use not intended by the manufacturer.

Some novel bilayer and trilayer tablet devices

A. Sustained release bilayer tablets:

The multilayered tablet concept has been long utilized to develop sustained release formulations. Such a tablet has a fast releasing layer and may contain bi- or triple layers to sustained the drug release. The pharmacokinetic advantage relies on the fact that drug release from fast releasing granules lead to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining granule. Among the different polymers, Eudragit and ethylcellulose have been used successfully to obtain appropriate sustained release matrix formulations of different materials[5].

B. Bilayer and floating-bioadhesive tablets:

A bilayer and floating-bioadhesive drug delivery system exhibiting a unique combination of floatation and bioadhesion to prolong residence in the stomach. The sustained layer was compressed and granules of the floating layer were added to it then both layers were compressed using a single station rotator press. Granules and tablets were characterized using a official method. The kind of the tablet exhibits independent regulation of buoyancy and drug release[6].

C. Bilayer caplets:

A bilayer caplets are excellent in two respect; firstly, single unit, such as bilayer caplets, excel in unit size than multiple unit, such as spansule capsules, and secondly, tablet shape changes from flat to capsule-like, namely caplets, that improves easiness in swallowing as compared with flat tablets[7].

D. Tablet in capsule devices:

This novel system is so-called ―tablet in capsule devices. The designed capsule device consists of an impermeable capsule body and a soluble cap. The multi-layered formulation prepared is filled within the capsule body and sealed with the water-soluble cap. Three-layered tablets, which serves as the first two pulses, a two-layered tablet or in powdered forms, which forms the third pulsatile drug release. Both multi-layer tables are inserted into an impermeable capsule body with a water-soluble cap, lactose filled in the bottom[8].

E. Three layered tablet system:

To allow biphasic drug release a three-layer tablet system has been developed. Two layers both contain a drug dose. An outer drug layer contains the immediately available dose of drug. An intermediate, made of swellable polymers, separates the drug layers. A film of an

impermeable polymer coats the layer containing the other dose of drug. The first layer can also involve a drug-free hydrophilic polymer barrier providing delayed (5h) drug absorption[9].

Bilayer problems[10]:

- Layer-separation.
- Insufficient hardness.
- Inaccurate individual layer weight control.
- Cross contamination between the layers.
- Reduced yield.

Bi-Layer tablets: Quality and GMP-requirement[10]:

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of-

- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.

- Providing sufficient tablet hardness.
- Preventing cross-contamination between the two layers.
- Producing a clear visual separation between the two layers.
- High yield.
- Accurate and individual weight control of the two layers.

Sustained Release Drug Delivery Systems:

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot, and repository dosage forms, are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of injectables dosage forms, these period may vary from days to months. In the case of orally administrated forms, however, these periods is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal tract. The term ―controlled release has became associated with those systems, from which therapeutic agents may be automatically delivered at predefined rates over a long period of time[11].

Design and Fabrication of Oral Sustained Release Drug Delivery System[12]:

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take consideration, the various pH that the dosage form would encounter during its transit, gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu. Theoretically

and desirably a sustained release delivery device, should release the drug by zero order process which would result in a blood level time profile similar to that after intravenous constant rate infusion

V

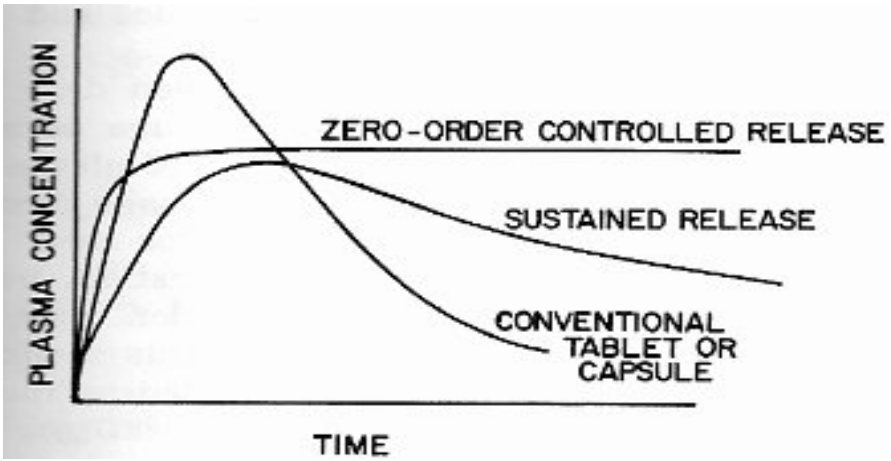


Fig-1: Plasma drug concentrations-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero-order controlled release formulation.

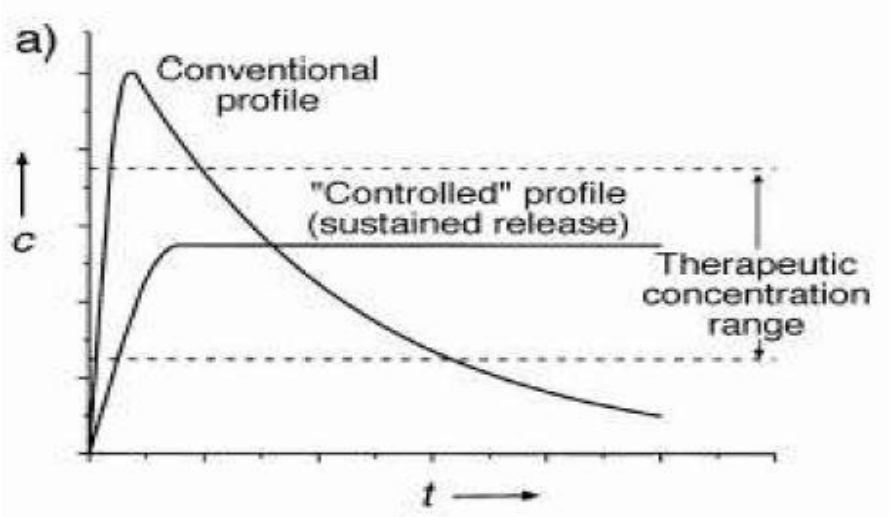


Fig-2: Comparison of conventional and controlled release profiles

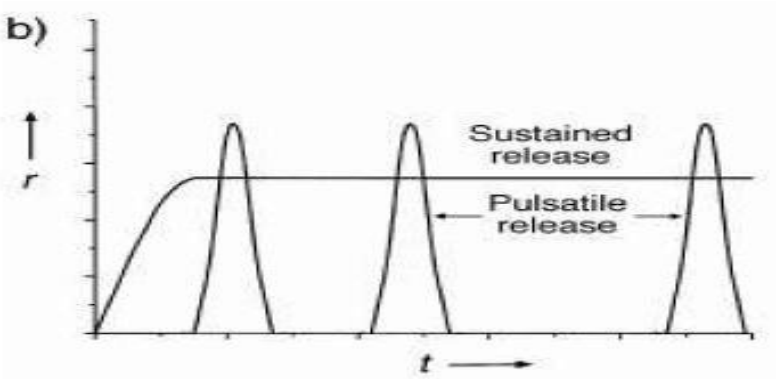


Fig-3: Dosage Regiem for conventional and controlled release systems

Sustained drug release has been attempted to be achieved, by following classes of sustained drug delivery system.

A) Diffusion sustained system.

i) Reservoir type.

ii) Matrix type

B) Dissolution sustained system.

i) Reservoir type.

ii) Matrix type

C) Methods using Ion-exchange.

D) Methods using osmotic pressure.

E) pH independent formulations.

F) Altered density formulations.

A] Diffusion sustained system:

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug J(in amount / area -time), across a membrane in the direction of decreasing

concentration is given by Fick‘s law.

J= - D dc/dx.

D = diffusion coefficient in area/ time

dc/dx = change of concentration 'c' with distance 'x'

In common form, when a water insoluble membrane encloses a core of drug, it must diffuse through the membrane, the drug release rate dm/ dt is given by,

dm/ dt= ADKD C/L

Where A = area

K = Partition coefficient of drug between the membrane and drug core

L= diffusion path length [i.e. thickness of coat]

Dc= concentration difference across the membrane.

1] Reservoir type:

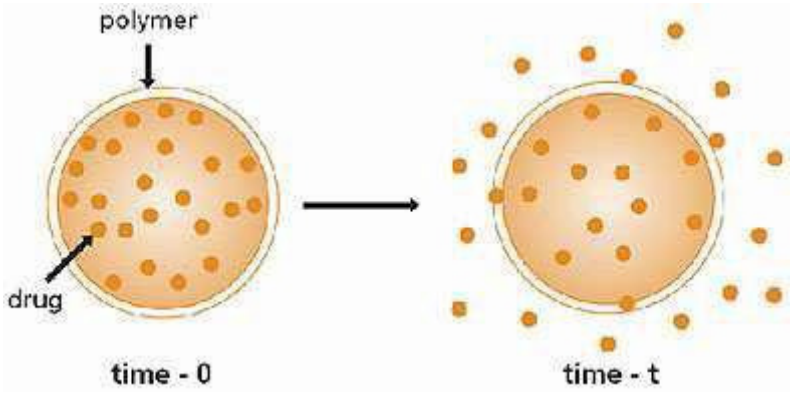


Fig-4: Schematic representation of diffusion sustained drug release: reservoir System

In the system, a water insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media.

Characterization

Description: Drug core surrounded by polymer membrane which controls release rate.

Advantages: Zero order delivery is possible, release rates variable with polymer type.

ii] Matrix type:

A solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution. *Higuchi* has derived the appropriate equation for drug release for this system,

$$Q = De/ T [2 A –eCs] Cst ½$$

Where;

Q = weight in gms of drug released per unit area of surface at time t

D = Diffusion coefficient of drug in the release medium

e = porosity of the matrix

Cs = solubility of drug in release medium

T= Tortuosity of the matrix

A = concentration of drug in the tablet, as gm/ ml

Characterization

Description: Homogenous dispersion of solid drug in a polymer mixture.

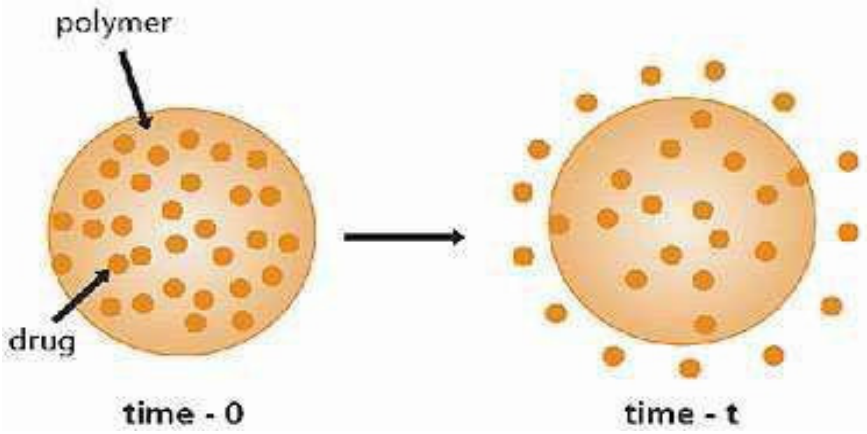


Fig-5: Schematic representation of diffusion sustained drug release: matrix system

A third possible diffusion mechanism is the system where a partially soluble membrane encloses a drug core. Dissolution of part of membrane allows for diffusion of the

constrained drug through pores in the polymer coat. The release rate can be given by following equation:-

Release rate = AD / L = [C1- C2]

Where, A = Area,

D = diffusion coefficient,

C1 = Drug concentration in the core,

C2 = Drug concentration in the surrounding medium,

L = diffusional path length

Thus diffusion sustained products are based on two approaches the first approach entails placement of the drug in an insoluble matrix of some sort. The eluting medium penetrates the matrix and drug diffuses out of the matrix to the surrounding pool for ultimate absorption. The second approach involves enclosing the drug particle with a polymer coat. In this case the portion of the drug which has dissolved in the polymer coat diffuses through an unstirred film of liquid into the surrounding fluid.

B] Dissolution sustained systems:

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation. These systems are most commonly employed in the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the device until it reaches the higher pH of the intestine. In most cases, enteric coated dosage forms are not truly sustaining in nature, but serve as a useful function in directing release of the drug to a special site.

i) Reservoir type:

Drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract. By alternating layers of drug with the rate controlling coats as shown in figure, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals. An alternative method is to administer the drug as group of beads that have coating of different thickness. This is shown in figure. Since the beads have different coating thickness, their release occurs in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at late times will be achieved from those with thicker coating.

i) Matrix type:

The more common type of dissolution from sustained dosage form as shown in figure.

It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

Two types of dissolution- sustained pulsed delivery systems:

a] Single bead– type device with alternating drug and rate-controlling layer.

b] Beads containing drug with differing thickness of dissolving coats

C] Methods using lon Exchange:

It is based on the formation of drug resin complex formed when a ionic solution is kept in contact with ionic resins. The drug from these complex gets exchanged in gastrointestinal tract and released with excess of Na+ and Cl- present in gastrointestinal tract

Resin + - Drug - + Cl- goes to resin + Cl- + Drug-

Where x- is cl- conversely

Resin - - drug+ + Na +goes resin – Na+ + Drug.

D] Methods using osmotic pressure:

A semi permeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of

the tablet through a small delivery aperture in tablet coating.

Two types of osmotically sustained systems are:-

Type A contains an osmotic core with drug

Type B contains the drug in flexible bag with osmotic core surrounding.

E] pH– Independent formulations:

The gastrointestinal tract present some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which constraint the length of prolongation, further the chemical environment throughout the length of gastrointestinal tract is constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH independent drug release. A buffered sustained release formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release e.g. propoxyphene in a buffered sustained release formulation, which significantly increase reproducibility.

F] Altered density formulations:

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

High density approach:

In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4gm/cm3.

Low density approach:

Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose.

Drug release mechanism from sustained release tablet[13]:

1. Zero-order release kinetics (Lazarus and Cooper, 1961)

$$Q(t) = k_0 t$$

Where Q(t) is the percent of drug dissolved as a function of time _t' in minutes

and k_0 describes the dissolution rate constant for zero-order release. A plot of the percent of drug released against time will be linear if the release obeys zero-order release kinetics. Values of release rate constant k_0 were obtained in each case from the slope of percent drug released versus time plots.

2. First-order release kinetics (Gibaldi and Feldman, 1967, Wagner, 1969)

$$\log Q_t = \log Q_0 + k_1 t / 2.303$$

The first-order equation describes the release from systems where release rate is concentration dependent. Where Q_0 is the initial amount of the drug, ‗t' is in minutes and k_1 describes the dissolution rate constant for first-order release kinetics. A plot of the logarithm of the percent drug remained against time will be linear if the release obeys first-order release kinetics.Values of release rate constant k_t were obtained in each case from the slope of the log percent drug remained versus time plots.

3. The simplified Higuchi model (Higuchi, 1961 and 1963)

$$Q(t) = k_H t^{1/2}$$

Where Q(t) is the percent of drug dissolved, time ‗t' in minutes, k_H is a dissolution rate constant for square root of time kinetics in percent dissolved $min^{-½}$.A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. Values of release of rate constant k_H were obtained in each case from the slope of the percent drug released versus square root of time plots.

4. The Fickian and non-Fickian drug release model (Korsmeyer et al, 1983)

In order to define a model, which will represent a better fit for the release from the tablet formulations, dissolution data up to 60% can be further analyzed using Peppas and Korsmeyer equation (power law). To evaluate the contribution of the release mechanisms other than diffusion, other models of the release kinetics were employed. Since erosion of the matrix will contribute to the release, a model describing general solute release from hydrophilic polymers as employed by the Korsmeyer et al (1983) was used. Applied to the hydrophilic polymers it has the simplified empirical form (Ford et al, 1991).

Equation.

Where k is the release rate and n is the release exponent. Values of the release exponent (n) and the kinetic constant (k) obtained in each case from the slope and y-intercept of a logarithmic plot of percent released versus time respectively. Peppas (1985) used this n value in order to characterize different release mechanisms.

3. REVIEW OF LITERATURE

Literature survey on formulation and evaluation of bilayer matrix tablet was carried out by referring various scientific journals, internet and helinet facility. A survey of literature reveals that extensive work was conducted employing hydrphylic and hydrophobic polymer to prepare matrix tablet.

- The present work aims to investing the possibility of sustaining the Losartan potassium release from matrix tablet, prepared by hydrophilic and hydrophobic polymer. The mechanism of drug release was diffusion coupled with erosion. It can be concluded that the polymer plays a major role in the design of sustained release matrix tablet. The study reveals that the release of drug is low when the matrix tablet contained hydrophilic and hydrophobic polymers as a combination than the other matrices and also shows anomalous(non-fickian) diffusion kinetics. Hence, it is clearly manifest the necessity of combining different classes of polymer is to get an acceptable pharmacokinetic profile in the fluctuating in vivo environment[14].

- The present study was to develop hydrophilic polymer and hydrophobic polymer based matrix Losartan potassium sustained release tablet which can release the drug up to time of 24 hrs in predetermined rate. Formulation of Losartan potassium matrix tablet was prepared by the polymer combination in order to get required theoretical release profile. Influence of hydrophilic and hydrophobic polymer on Losartan potassium was studied. Administration of LP in a sustained release dosage would be more desirable for antihypertensive effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration.(polymer)[15]

- The present study was to develop a sustained release matrix tablets of Losartan potassium, an anti hypertensive drug. The sustained release tablets were prepared by wet granulation.A decrease in release kinetics of the drug was observed on increasing polymer ratio. Applying exponential equation, all the formulation tablets(except F3) showed diffusion-dominated drug release. The mechanism of drug release from F3 was diffusion coupled with erosion.(polymer n release mec)[16]

- In the present research, an attempt has been made to formulate sustained release matrix tablet of nicorandil, a novel potassium channel opener used in cardiovascular disease. The tablets were prepared by wet granulation method and studied the effect of matrix former xanthan gum and guar gum separately. Tablets were evaluated for uniformity of weight, drug content, friability, hardness, thickness, in vitro dissolution and swelling study. The dissolution result shows that an increased amount of polymer resulted in retarded drug release[17].

- The present research work on bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bilayer tablet is better than the traditionally used mouthwash, sprays, gels. So use of bilayer tablet is a very different aspect for anti-inflammatory and analgesic. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet[19].

- The emerging new work on fixed dose combination of Metformin Hydrochloride (HCl) as sustained release and Glipizide as immediate release were formulated as a bilayer matrix tablet. Three different grades of (HPMC K 4M, HPMC K15M, HPMC K100M) were used. In vitro release studies were carried out with a phosphate buffer of pH 6.8 using USP dissolution apparatus 2 (paddle). Tablet thus formulated using HPMC K100M provided sustained release of Metformin HCl over a period of 10 hours. In-vitro release studies were carried out with a phosphate buffer of pH 6.8 using USP dissolution apparatus 2 (paddle). Tablet thus formulated using drug and carrier at 1:8 ratio provided immediate release of Glipizide over a period of 10 minutes[20].

- The present study was to prepare bi-layer tablet of Metoclopramide Hydrochloride (MTH) and Ibuprofen (IB) for the effective treatment of migraine. MTH and IB were formulated as immediate and sustained release layer respectively. The effect of concentration of hydrophilic matrix (HPMC K4M), binder (polyvinylpyrollidone [PVP K30]) and buffer (sodium bicarbonate) on IB release was studied[21].

- The objective of present investigation was to develop venlafaxine hydrochloride-layered tablets for obtaining sustained drug release. The tablets containing venlafaxine hydrochloride 150 mg were prepared by wet granulation technique using xanthan gum in the middle layer and barrier layers. The granules and tablets were characterized. The in vitro drug dissolution study was conducted in distilled water. The tablets containing two lower strengths were also developed using the same percentage composition of the middle layer. Kinetics of drug release was studied[21].

- The objective of present investigation was to develop dual component tablet made up of a sustained release and an immediate release layer was prepared by direct compression. A 32 full factorial design was applied to systematically optimize the drug release profile of the sustained release layer. The results of the full factorial design indicate that a small amount of HPMC K100M and a large amount of Ucarflock 302 favor sustained release of the metoclopramide hydrochloride vaginal dual component system[22].

- The present study was to a develop bilayer sustained release tablet of Isosorbide mononitrate, an anti-anginal organic nitrate vasodilator. The tablets were prepared by wet granulation method. Hydrophilic and hydrophobic matrix materials such as hydroxypropyl methylcellulose, and polyox were used, which can release the drug up to 24hrs in predetermined rate. The formulated tablet were also characterized by physical and chemical parameters such as for granules,angle of repose, bulk density, compressibility index, total porosity, and drug content and for the tablet thickness, hardness, diameter, weight variation test, drug content, friability, and in vitro release studies[23].

- The present investigation highlighted the formulation and optimization of losartan potassium tablets. To achieve this goal, various formulation of losartan potassium tablets were prepared and evaluated with respect to the various quality parameters both in process parameters for granules and parameters for finished products . On the basis of these parameters, the formula was optimized and compared with the innovator. It was observed that the optimized losartan potassium tablets was pharmaceutically equivalent with the innovator. The stability of optimized tablets at various atmospheric conditions was done and stability parameters were satisfactory[24].

- This work describes the development and validation of a dissolution test for 50 mg losartan potassium capsules using HPLC and UV spectrophotometry. A 2_4 full factorial design was carried out to optimize dissolution conditions and potassium phosphate buffer, pH 6.8 as dissolution medium, basket as apparatus at the stirring speed of 50 rpm and time of 30 min were considered adequate. Both dissolution procedure and analytical methods were validated and a statistical analysis showed that there are no significant differences between HPLC and spectrophotometry[25].

- The present study was to prepare twice daily sustained release matrix tablets of losartan potassium using Eudragit RLPO, RSPO and Ethyl cellulose individually and in combination of above polymers. Sustained release matrix tablets were developed using different drug polymer ratios and prepared by direct compression method. The influence different concentrations and nature of polymer was studied. Matrix tablets assessed for their physicochemical properties and invitro drug release studies. Drug-excipient interaction was evaluated by Differential scanning calorimetry and FTIR. There was no drug excipient interaction[26]

- The present study was to develop an optimised press-coated tablets of losartan potassium using an admixture of a hydrophilic polymer, hydroxypropylmethylcellulose (HPMC) and microcrystalline cellulose (MCC) in order to achieve a predetermined lag time for chronotherapy. The press-coated tablets (PCT) containing losartan potassium in the inner core were prepared by compression-coating with HPMC 100KM alone and admixed with MCC as the outer layer in different ratios. The effect of the outer layer on the lag time of drug release was investigated[27]

- This investigation was to prepare a gastroretentive drug delivery system of Losartan Potassium. Floating tablets of Losartan Potassium were prepared employing three different grades of HPMC K100, HPMC K15M and HPMC K4M by effervescent technique. The prepared tablets exhibited satisfactory physico-chemical characteristics. The tablet swelled radially and axially during in vitro buoyancy studies. HPMC K100 based matrix tablets showed significantly greater swelling indices compared with other batches[28]

- The objective of the study was to develop and evaluate controlled release bilayer matrix tablets of losartan potassium employing xanthan gum and gum karaya as a polymers. Controlled release bilayer matrix tablets containing losartan potassium were developed using different drug: polymer concentration. Tablets were prepared by direct compression method. Differential scanning calorimetry study revealed no chemical interaction between drug and polymers used. In-vitro release studies were carried out using USP XXIV type II (paddle method) dissolution apparatus at 75 rpm by taking 900 ml of 0.1 N HCl (pH 1.2) as dissolution medium for first 2 h and later replacing it with 900 ml pH 6.8 phosphate buffer solution for rest of the time period at 37±0.5oC. The mechanism of drug release was found to be non-fickian diffusion[29]

- The aim of the current study was to design oral controlled release matrix tablets of losartan potassium. Tablets were prepared by direct compression and evaluated for hardness, friability, thickness, drug content and in vitro dissolution parameters. Carbopol 934P and HPMC K 100M (hydroxyl propyl methyl cellulose) were used as the polymers . In vitro release studies were conducted in phosphate buffer pH 6.8 for 24 hours. The release profile of losartan potassium from all the formulations (except F2, F3, F8 which showed first order release) are close to zero order and follow diffusion dependent release. Irrespective of

the polymer type and its concentration, the prepared hydrophilic matrix tablets showed non-fickian (anomalous) release, coupled diffusion and polymer matrix relaxation as the values of release exponent (n) are in between 0.584 and 0.8692[30].

- The ultimate aim of the present study was to prepare twice daily sustained release matrix tablets of losartan potassium using Eudragit RLPO, RSPO and Ethyl cellulose individually and in combination of above polymers. Sustained release matrix tablets were developed using different drug polymer ratios and prepared by direct compression method. The influence different concentrations and nature of polymer was studied.In vitro release data shows individual low polymer concentration of RLPO, RSPO sustain the drug release up to 10hrs but combinations with EC sustain the drug release more than 12hrs.Eudragits in higher polymer proportion drug release was extend up to 12hrs. Ethyl cellulose has more retardation than Eudragits[31].

- The present investigation was to develop and evaluate Atorvastatin calcium (ATC) & Metoprolol succinate (MP) in same dosage form, so there is no need to take individual dosage form. The regioselective tablets were prepared by direct compression. Polyox WSR N-60K and HPMC K100M was used as hydrophilic polymers. The amount of polymer blends was optimized using 32 full factorial design. The swellings and in-vitro release were studied. Diffusion exponents (n) were determined for all the formulations (0.45-0.89), so predominant drug release mechanism is non-Fickian (anomalous) transport[32].

- The ultimate aim of the present study was hydrophilic matrix formulations are important and simple technologies that are used to manufacture sustained release dosage forms. Hydroxypropyl methylcellulose-based matrix tablets, with

and without additives, were manufactured to investigate the rate of hydration, rate of erosion, and rate and mechanism of drug release. The results revealed that the rate of hydration and erosion was dependent on the polymer combination(s) used, which in turn affected the rate and mechanism of drug release from these formulations. It was also apparent that changes in the microstructure of matrix tablets could be related to the different rates of drug release that were observed from the test formulations[33].

- The present investigation was Poly(carboxyalkyl methacrylates) were studied as a cationic-drug delivery system, at pH 6.8 and 8.0. Different polymer/ drug complexes were used to prepare compressed tablets. By kinetics experiments, we have found that drug release is dependent on both the hydrophobicity of the whole complex and the pH of the environment. Furthermore, a mechanism of dissociation/erosion clearly describes the drug release from a complex formed by a polymer soluble at target pH; otherwise, a mechanism of dissolution/diffusion is depicted. Additionally, we have observed that hydrophilic fillers increase the drug release rate[34]

- The emerging new work on fixed dose combination of metformin hydrocholride (HCl) as sustained release and glipizide as immediate release were formulated as a bilayer matrix tablet using hydroxy propyl methyl cellulose (HPMC) as the matrix-forming polymer, and the tablets were evaluated via in vitro studies. Three different grades of HPMC (HPMC K 4M, HPMC K 15M, and HPMC K 100M) were used. All tablet formulations yielded quality matrix preparations with satisfactory tableting properties. In vitro release studies were carried out at a phosphate buffer of pH 6.8 with 0.75% sodium lauryl sulphate w/v using the apparatus I (basket) as described in the United States Pharmacopeia (2000). The

release kinetics of metformin were evaluated using the regression coefficient analysis[35]

- The present examine on the release performance of two model drugs, diclofenac sodium and furosemide, from two- and three-layer drug delivery systems using as carriers hydrophilic swellable polymers, namely, Metolose, Polyox, Xantham gum, and an erodible material Gantrez. All prepared formulations demonstrated sustained release profiles. They also indicated that the carrier characteristics (particularly swelling-expansion, erosion-dissolution) and drug solubility in combination with tablet structure considerably influenced the performance of examined formulations as well as their mode and mechanisms of release[36].

- The present examine on multi-drug tablets of amlodipine besylate and atenolol were prepared as either mono-layer (mixed matrix) or bi--layer tablets containing each drug in a separate layer by using similar excipients and processing. Each tablet batch was packed in strip and blister packs and kept under accelerated temperature and humidity conditions. The stability of two tablet and packaging types was compared by HPLC analysis after 0, 1, 3 and 4.5 months and expressed as the content of intact amlodipine and atenolol. The study revealed that the bi-layer tablet formulation was more stable than the mono-layer type. Further, the stability was increased when the tablets were packed in aluminium strips as compared to PVC blisters[37]

- The objective of this study was to investigate the effect of lipophilic and hydrophilic components on the release of carbamazepine from granules and corresponding tablet. Wet granulation followed by compression.The matrix swelling behavior was investigated. It was found that increase in the concentration of HPMC results in reduction in the release rate from granules and

achievement of zero-order is difficult from the granules. The amount of HPMC plays a dominant role for the drug release. The release mechanism of CBZ from matrix tablet formulations follows non-Fickian diffusion shifting to Case II by the increase of HPMC content, indicating significant contribution of erosion. Increasing in drug loading resulted in acceleration of the drug release and in anomalous controlled-release mechanism due to delayed hydration of the tablets[38].

- Each of the proposed DLTs is composed of a fast-release layer and a sustained-release layer, anticipating rapid drug release that starts in the stomach to rapidly alleviate the symptoms and continues in the intestine to maintain protracted analgesic effect. An amorphous, freeze-dried inclusion complex of lornoxicam with hydroxypropyl-β-cyclodextrin, present in 1:2 (drug/cyclodextrin) molar ratio, was employed in the fast-release layer to enhance the dissolution of lornoxicam in the stomach and assure rapid onset of its analgesic effect. Xanthan gum (XG), a hydrophilic matrix-forming agent, was integrated in the sustained-release layer to provide appropriate sustainment of drug release. The weight ratios between the sustained-release layer and fast-release layer present in DLTs were adjusted to reach optimal formulations[39].

- The present work on a coated matrix tablet formulation has been used to develop controlled release diltiazem HCl (DIL) tablets. The developed drug delivery system provided prolonged drug release rates over a defined period of time. DIL tablets prepared using dry mixing and direct compression and the core consisted of hydrophilic and hydrophobic polymers such as hydroxypropylmethylcellulose (HPMC), Eudragits RLPO/RSPO, microcrystalline cellulose, and lactose. Tablets were coated with Eudragit NE 30D, and the influence of varying the inert hydrophobic polymers and the amount of the

coating polymer were investigated. The release profile of the developed formulation was described by the Higuchi model[40].

- The objective of this research work was to prepare and evaluate the effect of Eudragit RS PO and Eudragit RL PO polymers on the physical property and release characteristics of carbamazepine matrix tablets. Matrix tablets containing carbamazepine were prepared with Eudragit® RS PO alone as the rate-retarding polymer and also with a combination of Eudragit® RS PO and RL PO . The tablets were characterized for hardness as well as for carbamazepine release. The release data were subjected to different models in order to evaluate their release kinetics and mechanisms[41].

CHAPTER

4

MATERIALS AND METHODOLOGY

4. MATERIALS AND METHODS

4.1 MATERIALS.

Sl no	**Material**	**Source**
1	Losartan Potassium	kapl
2	Hydroxypropylmethylcellulose	yarrow chemicals pvt ltd
3	Eudragit Rspo	yarrow chemicals pvt ltd
4	Sodium Starch Glycolate	yarrow chemicals pvt ltd
5	Magnesium stearate	karnataka fine chem
6	Talc	karnataka fine chem

Equipment:

Sl no	Equipment	Source
1	Uv-visible spectrophotometer	Shimadzu-1700, shimadzu corporation, japan.
2	Electronic balance	Bl-220h, shimadzu corporation, japan
3	Ph meter	
4	Tablet punching machine	Cip, machinaries pvt. Ltd., ahmedabad
5	Sonicator	
6	Dissolution test apparatus	Electrolab, tdt-08l, dissolution tester(usp)
7	Fourier-transformed infrared spectrophotometer(ftir)	Perkin elmer spectrum gx

8	Hardness tester	pfizer
9	Friability apparatus	Electrolab, ed-2l(usp)
10	Disintegration apparatus	Electrolab, ed-2l(usp)
11	Programmable Stability test chamber	Thermo lab, India
12	Hot air oven	Servewell instruments, Bangalore

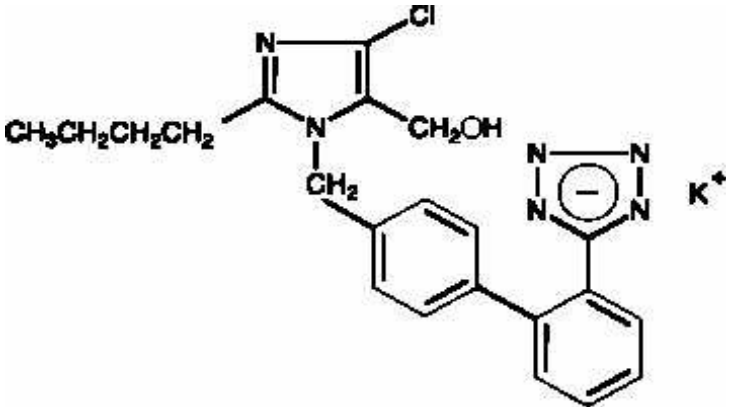
4.3 DRUG PROFILE

Losartan potassium

Chemical formula:

2 - butyl - 4 - chloro - 1 - [*p*- (*o* - 1 *H* - tetrazol - 5 - ylphenyl) benzyl] imidazole – 5 - methanol

Structural formula



Empirical formula: C22H22ClKN6O

Molecular weight: 461.01

Description: White or almost white powder.

Melting point: 263-264^{0}C.

Solubility: It is freely soluble in water and soluble in alcohols.

Half life: 2.5 hr

Drug category : anti hypertensive

Mechanism of action: Losartan potassium is an angiotensin II receptor antagonist. It suppresses the effects of angitensin II at its receptors, thereby blocking the

renninangiotensin system.The rennin-angiotensin system plays a crucial role in the control of blood pressure, and in particular it is felt to play crucial role in hypertension. Losartan has been demonstrated to be superior to previous peptide receptor antagonists and angiotensin converting enzyme (ACE) inhibitors because of its enhanced specificity, selectively, and tolerability.

Pharmacokinetics:

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively

Distribution

Both losartan and its active metabolite are 99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Elimination

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

METABOLISM

Under go substantial first pass metabolim by cyp-450 2c9 and 3A4 enzymes, fourteen of an oral dose is converted in to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonist activity.

Dose: 25, 50 and 100mg

Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- 2nd and 3rd Trimester of pregnancy
- Lactation
- Severe hepatic impairment

Adverse effect

Nervous system disorders:

Common: dizziness, vertigo

Uncommon: somnolence, headache, sleep disorders

***Cardiac disorder*:**

Uncommon: palpitations, angina pectoris

Vascular disorders:

Uncommon: symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash.

***Gastrointestinal disorders*:**

Uncommon: abdominal pain, obstipation

General disorders and administration site conditions:

Uncommon: asthenia, fatigue, oedema

Marketed Brands; LOSAR,COSAR

EXCIPIENTS PROFILE[40]

HYDROXYPROPYLMETHYLCELLULOSE

Non-proprietary names:

BP: Hypromellose

JP: Hydroxypropylmethylcellulose

PhEur: Hypromellosum

USP: Hypromellose

2 Synonyms

Benecel MHPC; E464; hydroxypropyl methylcellulose;

HPMC; Methocel; methylcellulose propylene glycol ether;

methyl hydroxypropylcellulose; Metolose; Tylopur

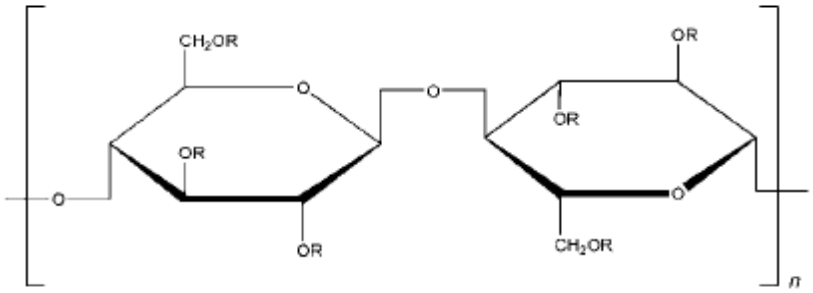
3 Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

4 Empirical Formula and Molecular Weight

hypromellose as a partly Omethylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Molecular weight is approximately 10 000 –1 500 000.

5 Structural Formula



where R is H, CH_3, or $CH_3CH(OH)CH_2$

6 Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation

or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.

In oral products, hypromellose is primarily used as a tablet binder,(1) in film-coating, (2–7) and as a matrix for use in extended-release tablet formulations.(8–12) Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules

Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

Examples of film-coating materials that are commercially available include AnyCoat C, Spectracel, and Pharmacoat

Hypromellose is also used as a suspending and thickening agent in topical formulations. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

8 Description

Hypromellose is an odorless and tasteless, white or creamywhite fibrous or granular powder.

Typical Properties

Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous

solution.

Ash: 1.5–3.0%, depending upon the grade and viscosity.

Autoignition temperature: 3608C

Density (bulk): 0.341 g/cm3

Density (tapped): 0.557 g/cm3

Density (true): 1.326 g/cm3

Melting point: browns at 190–200^0 C**;** chars at 225–2308C.

Glass transition temperature is 170–1808C.

Moisture content: hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air

9 Safety

Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect.

10 Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

POLYMETHACRYLATES(EUDRAGIT RSPO)

1 Nonproprietary Names

BP: Methacrylic acid–ethyl acrylate copolymer (1 : 1)

PhEur: Acidum methacrylicum et ethylis acrylas polymerisatum

1 : 1

USPNF: Ammonio methacrylate copolymer

Methacrylic acid copolymer

Methacrylic acid copolymer dispersion

2 Synonyms

Acryl-EZE; Acryl-EZE MP; Eastacryl 30D; Eudragit; Kollicoat

MAE 30 D; Kollicoat MAE 30 DP; polymeric methacrylates.

3 Chemical Name and CAS Registry Number

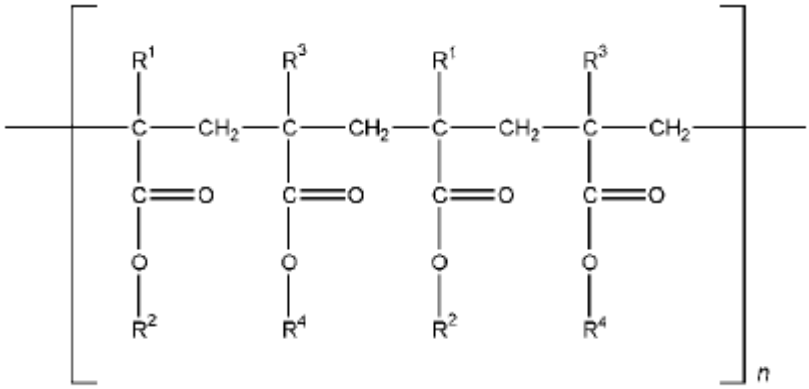
Poly(butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl

methacrylate) [24938-16-7]

4 Empirical Formula and Molecular Weight

The PhEur 2005 describes methacrylic acid–ethyl acrylate copolymer (1 : 1) as a copolymer of methacrylic acid and ethyl acrylate having a mean relative molecular mass of about 250 000. The ratio of carboxylic groups to ester groups is about 1 : 1. It may contain suitable surfactants such as sodium dodecyl sulfate or polysorbate 80. An aqueous 30% w/v dispersion of this material is also defined in a separate monograph. Polyacrylate dispersion (30 per cent) is described in the PhEur 2005 as a dispersion in water of a copolymer of ethyl acrylate and methyl methacrylate having a mean relative molecular mass of about 800 000. It may contain a suitable emulsifier. Typically, the molecular weight of the polymer is5100 000.

5 Structural Formula



6 Functional Category

Film former; tablet binder; tablet diluents

7 Applications in Pharmaceutical Formulation

or Technology

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents.(1–17) Depending on the type of polymer used, films of different solubility characteristics can be produced. Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5–20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct-compression processes in quantities of 10–50%.Polymethacrylate polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration

8 Description

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several

different types are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution. A (60 : 40) mixture of acetone and propan-2-ol is most commonly used as the organic solvent.

12 Incompatibilities

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature

14 Safety

Polymethacrylate copolymers are widely used as film-coating materials in oral pharmaceutical formulations. They are also used in topical formulations and are generally regarded as nontoxic and nonirritant materials. A daily intake of 2 mg/kg body-weight of Eudragit (equivalent to approximately 150mg for an average adult) may be regarded as essentially safe in humans.

SODIUM STARCH GLYCOLATE

1 Nonproprietary Names

BP: Sodium starch glycollate

PhEur:Carboxymethylamylum natricum

USPNF: Sodium starch glycolate

2 Synonyms

Carboxymethyl starch, sodium salt; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.

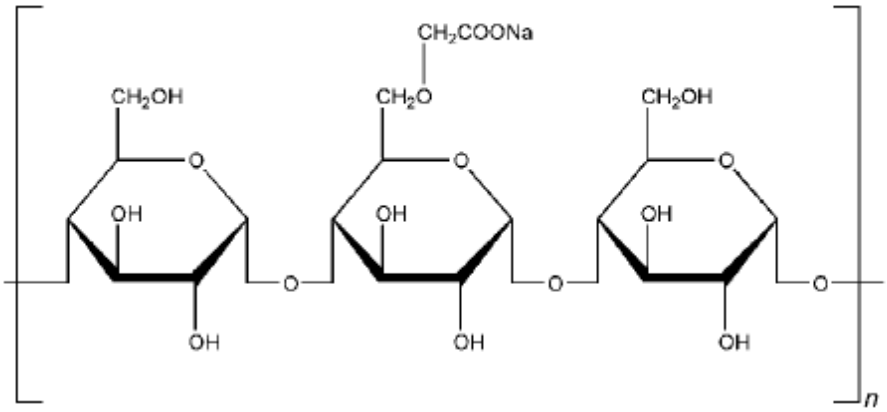
3 Chemical Name and CAS Registry Number

Sodium carboxymethyl starch [9063-38-1]

4 Empirical Formula and Molecular Weight

The USPNF 23 states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch, containing 2.8–4.2% sodium. The PhEur 2005 describes three types of material: Types A and B occur as the sodium salt of a cross-linked partly Ocarboxymethylated potato starch, containing 2.8–4.2% and 2.0–3.4% of sodium respectively. Type C is the sodium salt of a cross-linked by physical dehydration, partly O-carboxymethylated starch containing 2.8–5.0% sodium. Sodium starch glycolate may be characterized by the degree of substitution and crosslinking. The molecular weight is typically 5_105–1_106.

5 Structural Formula



6 Functional Category

Tablet and capsule disintegrant.

7 Applications in Pharmaceutical Formulation

or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule(1–6) and tablet formulations.(7–10) It is commonly used in tablets prepared by either direct compression(11–13) or wet-granulation processes.The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.(17–20). Increasing the tablet compression pressure also appears to have no effect on disintegration time.

8 Description

Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. The PhEur 2005 states that it consists of oval or spherical granules, 30–100 mm in diameter, with some less-spherical granules ranging from 10–35 mm in diameter.

9 Incompatibilities

Sodium starch glycolate is incompatible with ascorbic acid.

10 Safety

Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

MAGNESIUM STEARATE

BP: Magnesium stearate

JP: Magnesium stearate

PhEur: Magnesii stearas

USPNF: Magnesium stearate

2 Synonyms

Magnesium octa decanoate; octa decanoic acid, magnesium salt; stearic acid, magnesium salt.

3 Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

4 Empirical Formula and Molecular Weight

C36H70MgO4 591.34

5 Structural Formula

[CH3(CH2)16COO]2Mg

6 Functional Category

Tablet and capsule lubricant

7 Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams

8 Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin

9 Typical Properties

Crystalline forms: high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk): 0.159 g/cm3

Density (tapped): 0.286 g/cm3

Density (true): 1.092 g/cm3

Flash point: 2508C

Flowability: poorly flowing, cohesive powder.

Melting range:

117–1508C (commercial samples);

126–1308C (high purity magnesium stearate).

Solubility: practically insoluble in ethanol, ethanol (95%), ether

and water; slightly soluble in warm benzene and warm

ethanol (95%).

Specific surface area: 1.6–14.8m2/g

9 Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

10 Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following

TALC

1 Nonproprietary Names

BP: Purified talc

JP: Talc

PhEur: Talcum

USP: Talc

2 Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore. 3 Chemical Name and CAS Registry Number Talc [14807-96-6]

4 Empirical Formula and Molecular Weight

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small,

variable amounts of aluminum silicate and iron.

6 Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent,although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products.(4–6) Talc is also used as a lubricant in tablet formulations;(7) in a novel powder coating for extended-release pellets;(8) and as an adsorbant.(9) In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves; see Section 14. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties

8 Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness

9 Incompatibilities

Incompatible with quaternary ammonium compounds

10 Safety

Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. However However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs.(16–18) Contamination of wounds or body cavities with talc may also cause granulomas; therefore, it should not

be used to dust surgical gloves. Inhalation of talc causes irritation and may cause severe respiratory distress in infants

METHODS

Estimation of losartan potassium[41]:

In present study, the spectrophotometric method was adopted for the estimation of losartan potassium: using double beam U.V. spectrophotometer.

Preparation of Standard Stock Solution:

Stock solution: losartan potassium in methanol (100 mg in 100 ml).

Scanning: from the stock solution 4 µg/ml solution of losartan potassium was prepared in0.1 N Hcl(1.2 pH buffer) solution and scanned between 200-400nm. The absorption maxima of 234 nm was selected and used for further studies.

b) Standard calibration curve of losartan potassium in 0.1 N Hcl solution:

Preparation of standard stock solution:

Solution-A (1 mg/ml): 100 mg of Losartan potassium was accurately weighed and transferred into a 100 ml volumetric flask. The drug was then dissolved and diluted up to the mark with 0.1 N Hcl(1.2 pH buffer)

Solution-B (40 µg/ml): From solution-A, 4 ml was pipette and transferred into a 100 ml volumetric flask and diluted up to the mark with 0.1 N Hcl. From this solution-B, aliquots of 1.0, 2.0, 3.0, 4.0 and 5.0 ml were transferred to 10 ml volumetric flask and diluted up to the mark with 0.1N HCl buffer solution to contain 4, 8, 12, 16 and 20 µg/ml of losartan potassium respectively.

The absorbance was measured in the UV-Visible spectrophotometer at 234nm using 0.1N Hcl solution as blank and graph of concentration versus absorbance was plotted. . Standard plot data of losartan potassium in 0.1N Hcl solution is reported

Similarly the standard calibration curve of losartan potassium was prepared by using phosphate buffer pH 6.8 and & 7.4 by using above said method.

PREFORMULATION STUDIES.

Compatibility study

The compatability study was carried out for the losartan potassium, HPMC K 100M,EUDRAGIT RSPO and SSG alone and combinations at ambient condition and 40℃ / 75% RH for a period of one month and samples were subjected for FTIR and DSC study for their characterization of possible interaction b/w drug and career in solid state.

Fourier-transformation infrared (FTIR) spectroscopy:

Excipients are integral components of almost all pharmaceutical dosage forms. To investigate any possible interaction between the drug and the utilized polymers (HPMC K 100 M, EUDRAGIT RSPO,AND SSG), IR spectrum of pure drug (LOSARTAN POTASSIUM) and its physical mixture was carried by using FTIR the range selected was from 400cm-1 to 4000 cm-1

DSC study

Further the compatibility between drug and polymer was detected by DSC study. Thermograms were obtained by using a differential scanning calorimeter (NETZSCH, DSC 200PC, Japan) at a heating rate 10° C/min over a temperature range of 35-250° C. The sample was hermetically sealed in an aluminium crucible. Nitrogen gas was purged at the rate of 10 ml/min for maintaining inert atmospheres.

Trial batch for IR layer

Sr. No	Ingredients (mg/tab)	T1	T1	T1	T2	T2	T2	T3	T3	T3
1	Losartan potassium	25	25	25	25	25	25	25	25	25
2	Ssg	10	15	20	-	-	-	-	-	-
3	Cp	-	--	--	10	15	20	-	-	-
4	Ccs	-	-	-	--	-	-	10	15	20
5	lactose	50	50	50	50	50	50	50	50	50
6	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
7	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
8	%cdr	78.35	83.01	92.91	69.52	75.33	80.66	53.68	63.68	76.87

Trial batch for CR layer

Sr. No	Ingredients (mg/tab)	F-1	F-2	F-3	F4
1	Losartan potassium	84	84	84	84
2	Hpmc k 100m	30	30	30	30
3	Eudragit rs-100	30	--	--	--
4	Ec n-50	--	30	-	--
5	Carbomer	--	--	30	--
6	Eudragit rspo	--	--	--	30
7	Magnesium stearate	---	--	--	**--**
8	Talc	5	5	5	5
9	%cdr	72.73	78.53	83.19	90.98

OPTIMIZATION

The runs or formulations, which are designed based on factorial design, are evaluated for the response. The response values are subjected to multiple regression analysis to find out the relationship between the factors used and the response values obtained. The response values subjected for this analysis are;

1. Friability
2. Hardness
3. Percentage of Drug Release at 1st hour
4. Percentage of Drug Release at 8st hour.
5. Percentage of Drug Release at 12st hour

The duration of above responses were chosen for the analysis of the following relationship:

1. To study the effect of amount of SSG (10-20)

2. To study the effect of amount of HPMC K 100 M.(30-50)

3.To study the effect of amount of EUDRAGIT RSPO(30-50)

3. To study the combined effect of SSG, HPMC K 100 M. and EUDRAGIT RSPO

The multiple regression analysis was done using design expert 8.0.4.1 software, which is specially meant for this optimization process. The results of this analysis are presented in the table 5.4.1.

Using the regression coefficient of the factors, the polynomial equation for the response is constructed. Only significantly, contributing factors are considered for the equation generation.

Composition of losartan potassium sustained release layer.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
LOSARTAN POTASSIUM	84	84	84	84	84	84	84	84
HPMCK-100 (30 – 50mg)	30	30	50	50	30	50	50	30
EUDRAGIT RSPO (30 – 50mg)	50	30	50	30	30	30	50	50
MAGNESIUM STEARATE	5	5	5	5	5	5	5	5
TALC	5	5	5	5	5	5	5	5

Composition of losartan potassium immediate release layer.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
	25	25	25	25	25	25	25	25

LOSARTAN POTASSIUM								
SSG (10-20)	10	10	10	20	20	10	20	20
MAGNESIUM STEARATE	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
TALC	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Procedure for IR release layer granules for bilayer tablets of losartan potassium[42]:

Direct compression granulation method[43]

The drug, polymers and other excipients used for immediate (IR) layer was dried properly and passed through sieve # 80 and accurately weighed sufficient quantity .of components were thoroughly mixed in a porceline mortar for a period of 15 mins. The mixture were passed through # 20 and lubricated with magnesium stearate by further blend for 3 mins and finally talc was added to the blend which is ready for the compression.

Procedure for CR release layer granules for bilayer tablets of losartan potassium

Non aqueous Wet granulation

The drug, polymers and other excipients used for controlled release(CR) layer was dried properly and passed through sieve # 80 and accurately weighed sufficient

quantity .of components were premixed in a porceline mortar for a period of 10 mins. The powder mix was granulated by using 5% w/w isopropyl alcoholic solution . The granules were allowed to dry in ambient condition fallowed by subjected to tray drier at 40℃ until properly dried. The dried granules were passed through # 20 and lubricated with magnesium stearate by further blending for 3 mins and finally talc was added to the blend which is ready for the compression.

Compression of matrix tablets

LP granules of either immediate or sustained release granules subjected for compression using 8mm round flat punches of 12 station lab scale semi automatic rotary tablet punching machine(CIP, machinaries pvt. ltd., Ahmedabad).with appropriate speead and pressure, composition of all the batches were represented in table no

Compression of bilayer matrix tablets

The 75mg of equivalent weight of pre weighed LP granules of sustained release layer were first subjected in the die cavity and slightly compressed to adjust uniform spreading of the 25 mg of equivalent weight of pre weighed LP granules of Immediate release layer was subsequently placed in the die cavity and compressed with an constant pressure and speed.

postcompression parameters for immediate layers of losartan potassium

Postcompression parameters for sustained release layers of losartan potassium

Precompression parameters for Bilayer tablets containing immediate and sustained release layers of losartan potassium[44].

a) Angle of Repose

b) Bulk density and tapped density

c) Hausner ratio.

d) Carr's index

(a) Bulk density

Apparent bulk density ρ_b was determined by pouring the blend into a graduated cylinder. Thebulk volume (V_b) and weight of powder (M) was determined. The bulk density was calculated using the formula.

$$\rho_b = \frac{M}{V_b}$$

(b) Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using the formula.

$$\rho_t \quad \frac{M}{V_t}$$

(c) Compressibility index

The simplest way for measurement of flow of powder is its compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as follows

$$\text{I} = \frac{\rho_t - \rho_b}{\rho t} \times 100$$

Where, ρ_t = Tapped density, ρ_b = Bulk density

Compressibility index as an indication of powder flow properties

Carr's Index (%)	Type of Flow
>12	Excellent
12.0-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner ratio

Hausner ratio (HR) is an indirect index of ease of powder flow. It is calculated by the following formula

$$HR = \frac{Pt}{Pb}$$

Where, ρ_t is tapped density and ρ_b is bulk density.Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (> 1.25).

(e) Angle of repose

Angle of Repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a specified cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula

$$\tan \theta = h/r$$

$$\text{Therefore; } \theta = \tan^{-1}$$

Where, θ is Angle of Repose; h is height of cone; r is radius of cone

Angle of Repose(°)	Type of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Evaluation of Postcompression parameters for immediate and sustained bilayer tablet of losartan potassium[45].

a) Hardness

b) Thickness

c) Weight variation,

d) Friability

e) Drug content uniformity

f) In vitro drug release studies.

G) swelling study

h) stability study

Tablet Thickness and size[45]

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using venire caliper.

Tablet Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in kg/cm2.

Friability

Friability is the measure of tablet strength. Electrolab EF-2 friabilator (USP) was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined.

% loss = [(Initial wt. of tablets – Final wt. of tablets)/ Initial wt. of tablets] ×100

Uniformity of weight

Twenty tablets were selected at random and the average weight was calculated. Weight Variation was calculated and was compared with I. P. standards.

Determination of drug content[46]

Three tablets were powdered and powder equivalent to weight of one tablet (100mg) was transferred to 100ml volumetric flask containing distilled water. For ensuring complete solubility sonication was done for 30 mins.Solution was suitably diluted and the absorbance was determined by UV-Visible spectrophotometer at 250nm.

Disintegration test (DT) [47]

In vitro drug release studies[16]

The prepared matrix tablets were subjected to *in-vitro* dissolution studies using an 8

station USP dissolution apparatus (Electrolab, TDT-08L, Dissolution tester USP). The dissolution studies were carried out in pH 1.2 for 3 hrs, in pH 6.8 for 4 hr & pH 7.4 for 4 hrs at 37 ± 0.5^0 c and 50 rpm . At regular time interval, 5 ml of sample was withdrawn from the dissolution medium and replaced with equal volume of methanol. After filtration and appropriate dilution, the samples were analyzed at 234 nm for losartan potassium against blank using UV-Visible spectrophotometer. The amount of drug present in the samples was calculated using standard curve.

Data analysis[48]:

The dissolution profile of most satisfactory formulation was fitted to zero order, first order and Higuchi model to ascertain the kinetic modeling of the drug release. The methods were adopted for deciding the most appropriate model.

Cumulative percent drug released versus time (Zero order kinetic model)

Log cumulative percent drug remaining versus time (First order kinetic model)

Cumulative percent drug released versus square root of time (Higuchi's model).

Log percentage drug released Vs log time (Peppas plots)

- **Zero order release rate kinetics:**

To study the Zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K.t$$

Where 'F' is the fraction of drug release, 'K' is the release rate constant and't' is the release time.

When the data is plotted as cumulative percent drug release versus

time, if the plot is linear then the data obeys Zero-order release kinetics, with a slope equal to K_0.

- **Higuchi release model:**

To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$$F = K . t_{1/2}$$

Where, 'F' is the amount of drug release,

'K' is the release rate constant, and

't' is the release time.

When the data is plotted as a cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

- **Korsmeyer and Peppas release model:**

The release rate data were fitted to the following equation,

$$M_t / M_\infty = K. t^n$$

Where, M_t / M_∞ is the fraction of drug release, 'K' is the release constant,'t' is the release time, and 'n' is the diffusion exponent for the drug release that is dependent on the shape of the matrix dosage form

The value of release exponent (n) was found to be a function of polymer used and the physicochemical property of a drug molecule itself.

Kinetic results revealed that, all the formulations followed zero order kinetics as correlation coefficient (r2) values (0.9738-0.9921) are higher than that of first order release kinetics.

The prepared hydrophilic bilayer matrix tablets showed Non-Fickian (anomalous) release, as the values of release exponent (n) lies between 0.5594-0.8662 with their correlation coefficient (r2) values between 0.9778-0.9985, indicating that coupled diffusion, polymer swelling and relaxation were involved in the release process

swelling study[azar]

The extent of swelling was measured in terms of % weight gain by the tablet. One tablet from each formulation was weighed and kept in Petri dish containing 20 ml of phosphate buffer of pH 6.8. At the end of specified time intervals tablets were withdrawn from Petri dish and excess buffer blotted with tissue paper and weighed.

The % weight gain by the tablet was calculated by formula:

$$\%\text{Swelling index} = \frac{M_t - M_0}{M_t} \times 100$$

Where, M_t – weight of tablets at time‘t’; M_0 – weight of tablets time‘0’

Stability Studies:

STABILITY OF A DRUG CAN BE DEFINED AS THE TIME FROM THE DATE OF MANUFACTURE AND THE PACKAGING OF THE FORMULATION, UNTIL ITS CHEMICAL OR BIOLOGICAL ACTIVITY IS NOT LESS THAN A PREDETERMINED LEVEL OF LABELED POTENCY AND ITS PHYSICAL CHARACTERISTICS HAVE NOT CHANGED APPRECIABLY OR DELETERIOUSLY.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a re-test

period for the drug substance or a shelf life for the drug product and recommended storage conditions.

The International Conference on Harmonization (ICH) guidelines titled "Stability Testing of New Drug substance and Products" (QIAR2) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America.

ICH specifies the length of study and storage conditions.

Long-term Testing: 25^0C 2^0C/60 % RH ± 5% for 3 Months.

Accelerated Testing: 40^0C ± 2^0C/75 % RH ± 5% for 3 Months.

Method

The selected formulations were packed in amber- colored bottles, which were tightly plugged with cotton and capped with aluminum. They were then stored at 25 ºC / 60% RH, and 40 ºC / 75% RH for 90 days and evaluated for their hardness, friability, drug content, disintegration time and *in vitro* dissolution study.

CHAPTER

5

RESULTS

5. RESULTS

5.1 Preformulation Studies:

5.1.1 Organoleptic Properties:

a) Colour: A small quantity of Losartan potassium powder was taken in butter paper and viewed in well-illuminated place.

b) Taste and odour: Very less quantity of Losartan potassium was used to get taste with the help of tongue as well as smelled to get the odour.

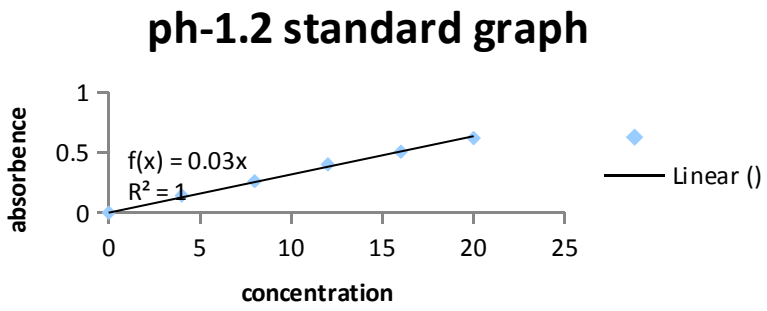
Table no: 12 Organoleptic Properties for Losartan potassium

Test	Specification/limits	Observations
Colour	White	White
Taste	Bitter	Bitter
Odour	Odourless	Odourless

STD Calibration curve of losartan potassium in 1.2 ph solution

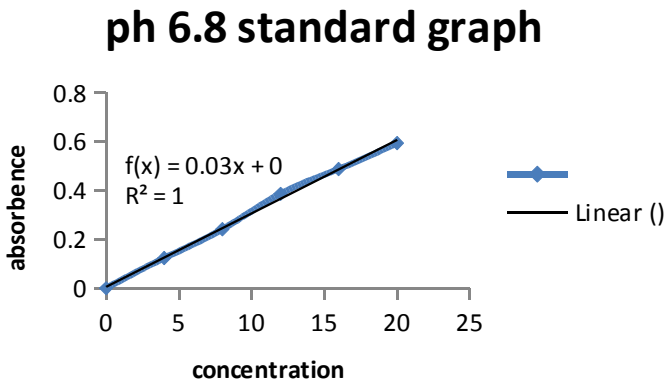
Concentration (µgm/ml)	Absorbance (mean ± Sd)
0	0.00 ±0.00
4	0.144 ±0.005
8	0.262±0.004
12	0.403±0.003
16	0.506±0.004
20	0.62± 0.005

*Average of three determinations



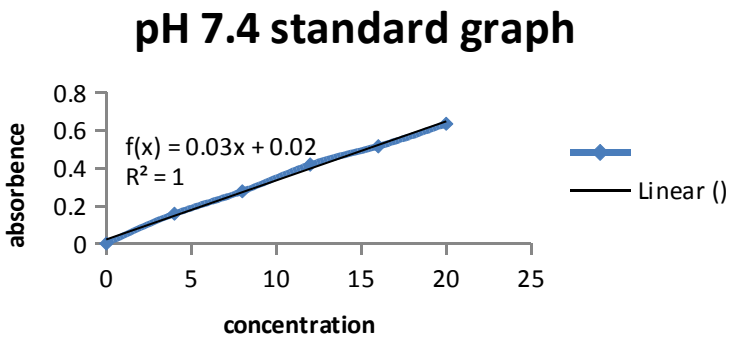
Calibration curve of losartan potassium in 6.8 ph solution

Concentration (µgm/ml)	Absorbance (mean ± Sd)
0	0.00
4	0.123
8	0.241
12	0.386
16	0.487
20	0.593



Calibration curve of losartan potassium in 7.4 ph solution.

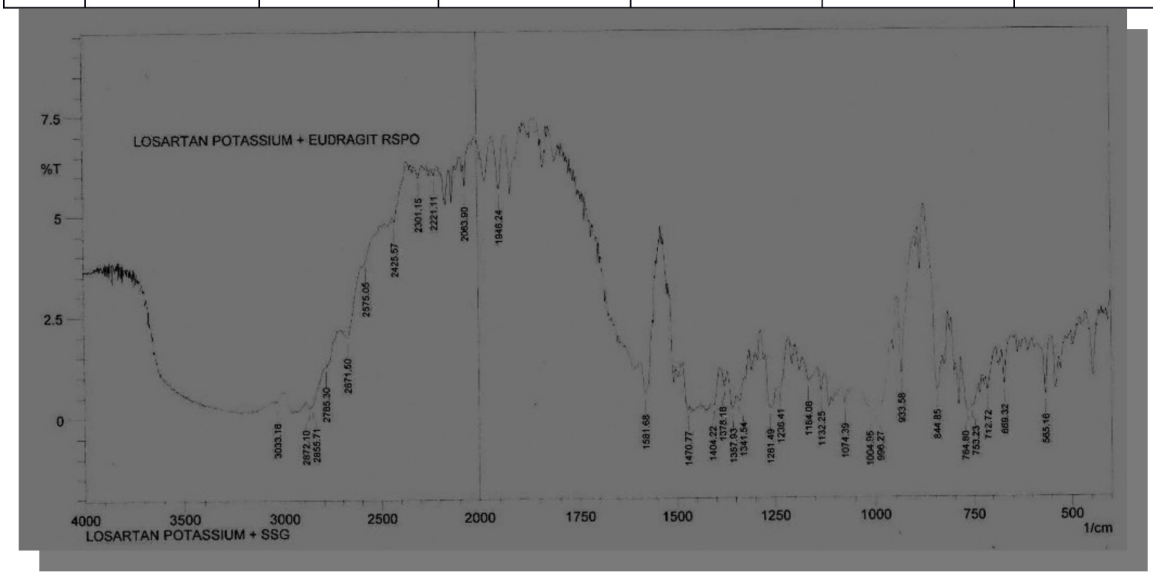
Concentration (µgm/ml)	Absorbance (mean ± Sd)
0	0.00
4	0.157
8	0.276
12	0.418
16	0.515
20	0.634



Compatibility studies of losartan potassium with the exiepient.

Pure losartan potassium		
Functional group	**Range**	**Observed range in pure drug**
C=N stretching	1515-1590	1575
OH	1160 -1270	1259
1,4 di substituted phenyl ring	800-850	842
1,6 substituted phenyl ring	720-780	763
C-Cl	550-850	560

Sl no.	Name of pure drug	Standard value of drug(cm-1)	Observed value of SSG with drug(cm-1)	Observed value of eudragit rspo with drug(cm-1)	Observed value of hpmc k100m with drug(cm-1)	Observed value of polymer combination with drug(cm-1)
1	Losartan potassium	1515-1590	1581	1575	1580	1575
		1160 -1270	1164	1550	1258	1259
		800-850	844	844	844	845
		720-780	764	762	762	762
		550-850	565	565	565	565



Post compression study of IR layer

SL. No	TESTS	Specification	T-1a	T-1b	T-1c
1.	Thickness				

	(mm)*	3.42 – 3.98 mm	3.42±0.05	3.44±0.01	3.46±0.005
2.	Hardness* (kg/cm^2)	5.0 - 6.0 kg/cm^2	5.3±0.25	5.3±0.20	5.1±0.35
3.	Friability* (%)*	Not more than 1%	0.25±0.04	0.30±0.02	0.25±0.04
4.	Average weight* (mg)	90- 100 mg	90	95	100
5.	Weight variation*	± 7.5% from the average weight	2.0%	1.2%	2.1%

SL. No	**TESTS**	**Specification**	**T-2a**	**T-2b**	**T-2c**
1.	Thickness (mm)*	3.42 – 3.98 mm	3.45±0.05	3.41±0.01	3.46±0.005
2.	Hardness* (kg/cm^2)	5.0 - 6.0 kg/cm^2	5.4±0.22	5.4±0.19	5.2±0.25
3.	Friability* (%)*	Not more than 1%	0.25±0.04	0.30±0.02	0.25±0.04
4.	Average weight* (mg)	90- 100 mg	90	95	100
5.	Weight variation*	± 7.5% from the average weight	2.0%	1.2%	2.1%

SL. No	TESTS	Specification	T-3a	T-3b	T-3c
1.	Thickness (mm)*	3.42 – 3.98 mm	3.45±0.05	3.44±0.01	3.47±0.005
2.	Hardness* (kg/cm^2)	5.0 - 6.0 kg/cm^2	5.3±0.25	5.3±0.20	5.1±0.35
3.	Friability* (%)*	Not more than 1%	0.25±0.04	0.30±0.02	0.25±0.04
4.	Average weight* (mg)	90- 100 mg	90	95	100
5.	Weight variation*	± 7.5% from the average weight	2.0%	1.2%	2.1%

Post compression study of CR layer

SL. No	TESTS	SPECIFICATION	F-1	F-2	F-3	F-4
1.	Thickness (mm)*					

		3.42 – 3.78 mm	3.59±0.05	3.64±0.01	3.56±0.005	3.58±0.01
2.	Hardness* (kg/cm^2)	5.0 - 7.0 kg/cm^2	6.3±0.25	6.5±0.20	6.1±0.35	6.3±0.26
3.	Friability* (%)*	Not more than 1%	0.35±0.04	0.30±0.02	0.45±0.04	0.41±0.01
4.	Average weight* (mg)	150 mg	150	150	150	150
5.	Weight variation*	± 7.5% from the average weight	2.0%	1.2%	2.1%	1.2%

Precompression parameters for Losartan potassium fast dissolving layer.

Batch code	Bulkdensity (gm/cm^3)	Tappeddensity (gm/cm^3)	Carr'sindex (I_C)	Hausnerratio (H_R)	Angel of repose(θ)
F1	0.51	0.59	13.5	1.15	30.21
F2	0.48	0.55	12.7	1.14	31.23
F3	0.46	0.52	11.5	1.13	29.56
F4	0.47	0.53	11.3	1.12	27.58
F5	0.48	0.56	14.2	1.16	28.42
F6	0.5	0.58	13.79	1.16	29.78
F7	0.46	0.55	16.36	1.19	30.11
F8	0.45	0.53	15.09	1.17	30.29

Precompression parameters for losartan potassium sustained release layer.

Batch code	Bulkdensity (gm/cm^3)	Tappeddensity (gm/cm^3)	Carr'sindex (I_C)	Hausnerratio (H_R)	Angel of repose(θ)
F1	0.467 ± 0.29	0.5914 ± 0.19	21.9 ±0.13	1.26±0.16	30.6 ±0.28
F2	0.478 ±0.32	0.598 ± 0.27	20 ± 0.17	1.25±0.17	29.1 ±0.25
F3	0.447 ± 0.39	0.573 ± 0.32	21.9 ±0.23	1.28±0.14	29.7 ±0.23
F4	0.469 ± 0.25	0.59 ± 0.19	20.5 ±0.31	1.25±0.14	29.3 ±0.23
F5	0.469 ± 0.27	0.577 ± 0.39	18.5 ±0.33	1.23±0.12	27.7 ±0.35
F6	0.449 ± 0.31	0.555 ± 0.15	18.9 ±0.41	1.23±0.16	27.3 ±0.25
F7	0.465 ± 0.42	0.552 ± 0.27	15.7 ±0.28	1.18±0.13	26.4 ±0.55
F8	0.472 ± 0.4	0.589 ± 0.3	19.8 ±0.09	1.24±0.19	29.6 ±0.43

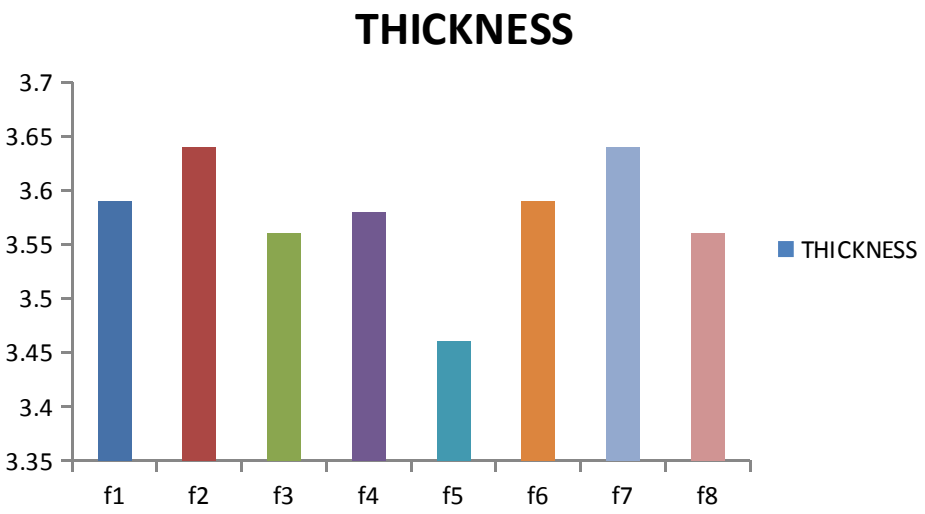
Evaluation parameters of bilayer layer matrix tablet.

SL. No	TESTS	SPECIFICATION	F-1	F-2	F-3	F-4
1.	Thickness (mm)*	3.42 – 3.78 mm	3.59±0.05	3.64±0.01	3.56±0.005	3.58±0.01
2.	Hardness*		6.3±0.25	6.5±0.20	6.1±0.35	6.3±0.26

	(kg/cm^2)	5.0 - 7.0 kg/cm^2				
3.	Friability* (%)*	Not more than 1%	0.25±0.04	0.30±0.02	0.25±0.04	0.21±0.01
4.	Average weight* (mg)	203- 253 mg	223	203	243	233
5.	Weight variation*	± 7.5% from the average weight	2.0%	1.2%	2.1%	1.2%

SL. No	**TESTS**	**SPECIFICATION**	**F-5**	**F-6**	**F-7**	**F-8**
1.	Thickness (mm)*	3.42 – 3.78 mm	3.46±0.02	3.59±0.04	3.64±0.02	3.56±0.01
2.	Hardness* (kg/cm^2)	5.0 - 7.0 kg/cm^2	6.5±0.25	6.3±0.43	6.5±0.503	6.1±0.15
3.	Friability* (%)*	Not more than 1%	0.25±0.03	0.40±0.04	0.41±0.05	0.35±0.03
4.	Average weight* (mg)	203- 253 mg	213	223	253	233
5.	Weight variation*	± 7.5% from the average weight	2.1%	2.0%	1.2%	2.1%

Where, * All values are mean ± SD, n =3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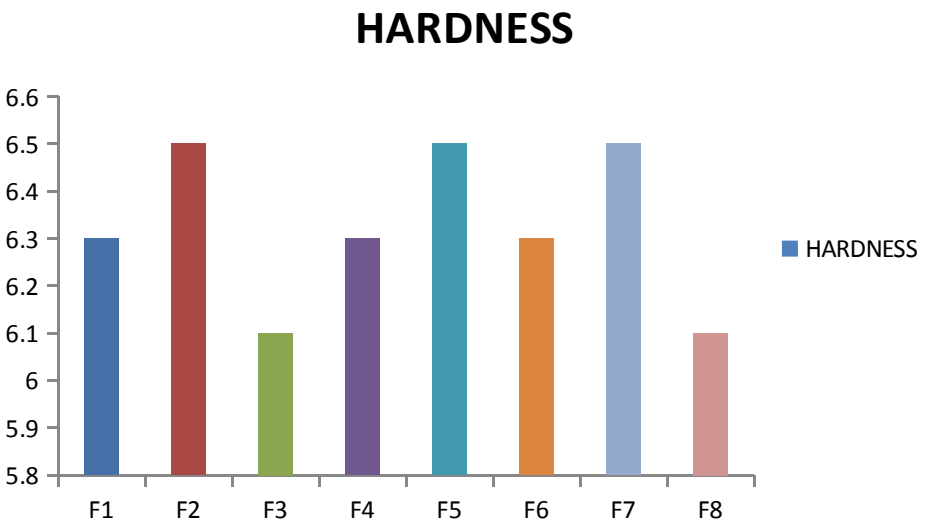
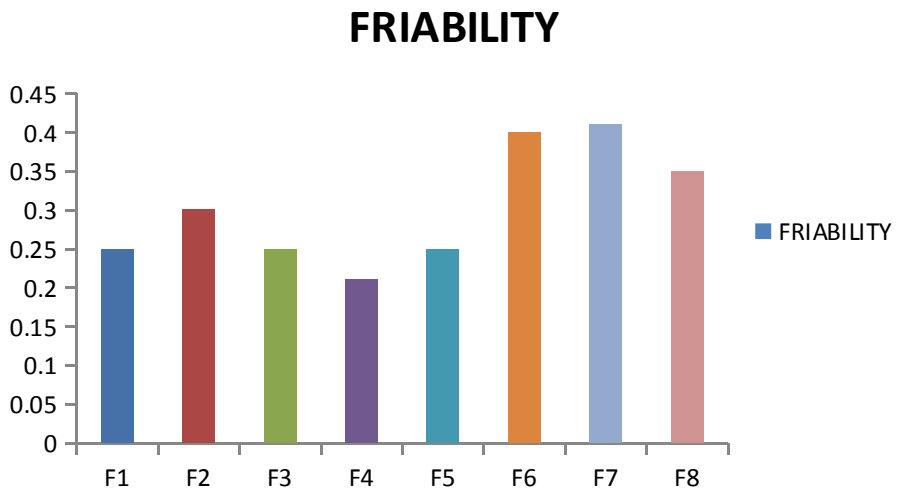
3.7
3.65
3.6
3.55
3.5
3.45
3.4
3.35
f1
f2
f3
f4
f5
f6
f7
f8
THICKNESS


HARDNESS
6.6
6.5
6.4
6.3
6.2
6.1
6
5.9
5.8
F1
F2
F3
F4
F5
F6
F7
F8
HARDNESS



5.6.3 Drug Content:

Table no. 18. Drug Content Uniformity of tablet formulations (F1-F8)

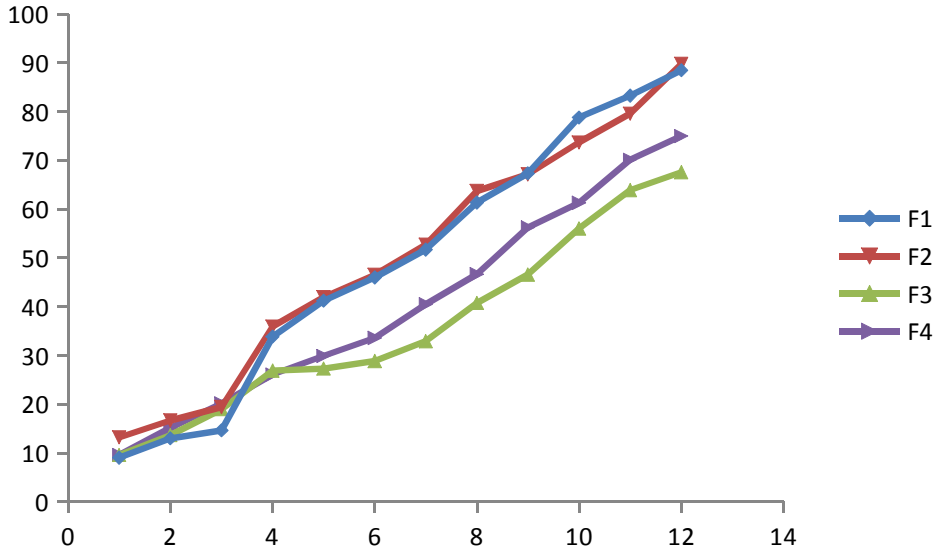
Formulations Code	% Drug Content*
F-1	99.66±0.62
F-2	97.5±0.76
F-3	99.16±0.47
F-4	99.66±0.60
F-5	99.66±0.33
F-6	99.9±0.33
F-7	98.16±0.34
F-8	99.16±0.47

Where,

**** All values are mean ± SD, n =3.***

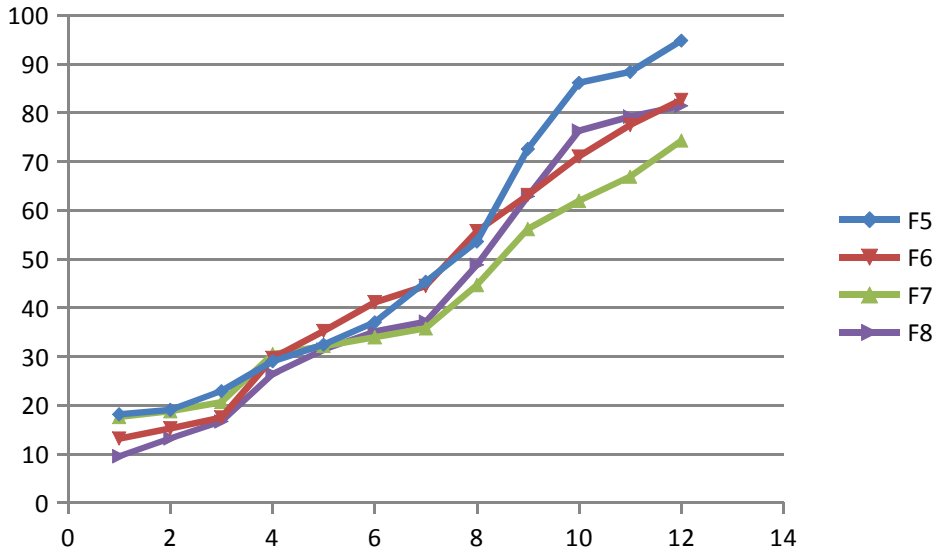
TIME(hr)	%CDR				
	F1	**F2**	**F3**	**F4**	

0	**0**	**0**	**0**	**0**	
1	**9.005**	**13.17**	**9.54**	**9.54**	
2	**12.98**	**16.60**	**13.62**	**15.10**	
3	**14.63**	**19.38**	**18.94**	**20.02**	1.2 ph
4	**33.83**	**35.91**	**26.83**	**26.02**	
5	**41.19**	**41.91**	**27.28**	**29.85**	
6	**45.96**	**46.47**	**28.80**	**33.53**	
7	**51.67**	**52.67**	**32.89**	**40.46**	6.8 ph
8	**61.33**	**63.69**	**40.73**	**46.62**	
9	**67.32**	**67.11**	**46.55**	**56.19**	
10	**78.75**	**73.64**	**55.99**	**61.25**	
11	**83.25**	**79.53**	**63.88**	**70.10**	
12	**88.44**	**89.75**	**67.54**	**74.96**	7.4 ph



	%CDR	

TIME(hr)					1.2 ph
	F5	F6	F7	F8	
0	0	0	0	0	
1	18.14	13.17	17.60	9.54	
2	19.05	15.26	18.78	13.22	
3	22.92	17.49	20.63	16.65	
4	29.03	29.71	30.48	26.41	
5	32.42	35.26	32.15	31.43	
6	37.04	41.12	33.96	35.14	
7	45.31	44.46	35.78	37.12	6.8 ph
8	53.58	55.71	44.68	48.83	
9	72.57	63.16	56.16	62.88	
10	86.16	71.06	61.92	76.32	
11	88.40	77.52	66.90	79.22	
12	94.82	82.67	74.32	81.47	7.4 ph



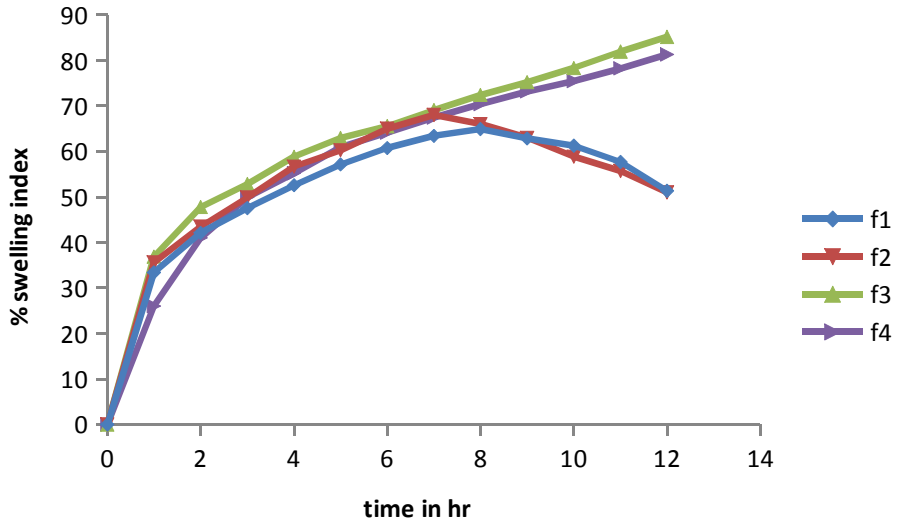
BATCH CODE	Regression analysis and correlation coefficient							
	Zero order		First order		Higuchi		Korsmeyer peppas	
	r^2	N	r^2	N	r^2	n	r^2	N
F1	0.982	7.668	0.942	0.066	0.882	28.08	0.914	1.641
F2	0.979	7.387	0.981	7.208	0.975	34.10	0.943	1.578
F3	0.969	5.219	0.975	5.288	0.892	19.54	0.965	0.790
F4	0.989	5.982	0.955	0.075	0.907	22.28	0.983	0.840
F5	0.982	7.668	0.942	0.066	0.882	28.08	0.914	1.641
F6	0.995	6.768	0.945	0.054	0.904	24.77	0.993	1.056
F7	0.968	4.935	0.934	0.035	0.907	18.93	0.958	0.734

F8	**0.976**	**7.807**	**0.887**	**0.075**	**0.872**	**27.98**	**0.973**	**1.001**

Swelling study of bilayer matrix tablets of losartan potassium

Time (hrs)	**% Swelling study**							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	**33.43**	**35.55**	**36.88**	**26.03**	**27.79**	**35.29**	**37.15**	**34.54**
2	**42.07**	**43.45**	**47.74**	**41.01**	**40**	**46.31**	**46.23**	**43.56**
3	**47.52**	**49.87**	**52.81**	**49.89**	**48.04**	**53.97**	**49.23**	**49.23**
4	**52.55**	**56.62**	**58.81**	**55.19**	**55.43**	**59.63**	**53.15**	**53.91**
5	**57.11**	**60.19**	**62.90**	**60.84**	**59.42**	**64**	**56.85**	**56.45**
6	**60.73**	**65**	**65.53**	**64.09**	**64.37**	**67.11**	**61.19**	**60.19**
7	**63.38**	**67.98**	**69.04**	**67.41**	**69.52**	**70.27**	**65.43**	**64.39**

8	64.88	65.99	72.38	70.34	63.00	64.63	69.37	67.89
9	62.83	62.95	75.19	73.14	59.9	62.06	73.43	63.13
10	61.21	58.82	78.28	75.42	57.14	57.28	77.13	59.91
11	57.68	55.67	81.89	78.19	53.26	53.19	81.54	54.21
12	51.31	50.96	85.15	81.24	46.00	46.34	84.29	49.93



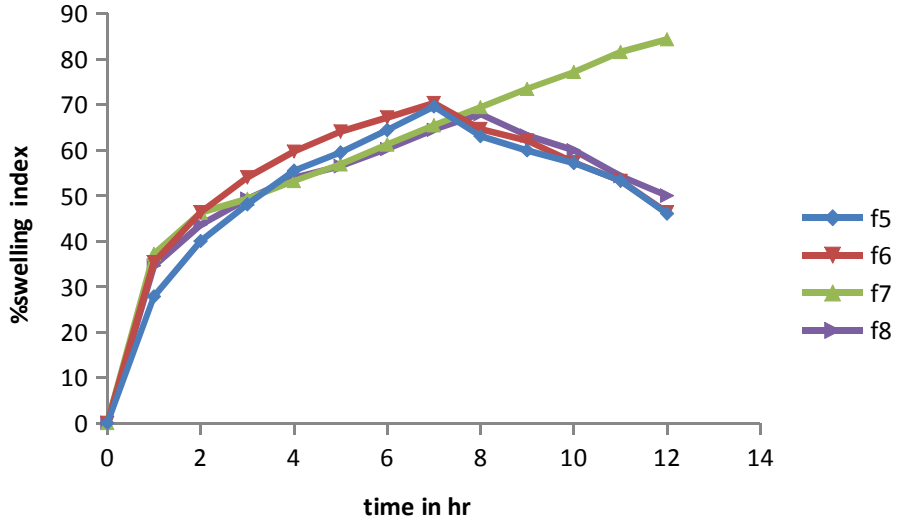

90
80
70
60
50
40
30
20
10
0
%swelling index
0
2
4
6
8
10
12
14
time in hr
f5
f6
f7
f8

Table 5.4.1 Design and Summary Response Data

Run	SSG	HPMC k-100 m	EUDRAGIT RSPO	Hardness (Kg/cm²)	Friability (%)	n VALUE
1	10	30	30	6.3	0.25	1.641
2	20	50	30	6.5	0.30	1.578
3	10	30	50	6.1	0.25	0.79
4	20	30	50	6.3	0.21	0.84
5	20	30	30	6.5	0.25	1.0
6	10	50	50	6.3	0.40	1.0
7	20	50	50	6.5	0.41	0.734
8	10	50	30	6.1	0.35	1.0

SSG: Sodium Starch Glycolate

Run	SSG	HPMC k-100 m	EUDRAGIT RSPO	%CDR at 1 (hr)	%CDR at 8 (hr)	%CDR at 12 (hr)
1	10	30	30	9.72	61.33	88.44
2	20	50	30	13.17	63.69	89.75
3	10	30	50	9.54	40.73	67.54
4	20	30	50	9.54	46.62	74.96
5	20	30	30	18.14	53.58	94.82
6	10	50	50	13.17	55.71	82.67
7	20	50	50	17.60	44.69	74.32
8	10	50	30	9.54	48.83	81.47

Response: R1 (hardness)

5.4.1.1(a) ANOVA for factorial model

Source	Sum of Squares	DF	Mean Square	F Value	Prob >F
Model	**0.50**	**1**	**0.50**	**6.0**	**0.0498**
A-SSG	0.50	1	0.50	6.0	0.0498
Residual	0.50	6	0.083	-	-
Cor Total	1.0	7	-	-	-

Table 5.4.1.1(b) Estimated Regression Coefficients

Factor	Coefficient Estimate	DF
Intercept	4.0	1
A- **SSG**	-0.25	1

Final Equation in Terms of Coded Factors:

R1 = Hardness =+4.00-0.25 * A

Figure 5.4.1.1(a): Correlation between actual and predicted values for Friability (R1)

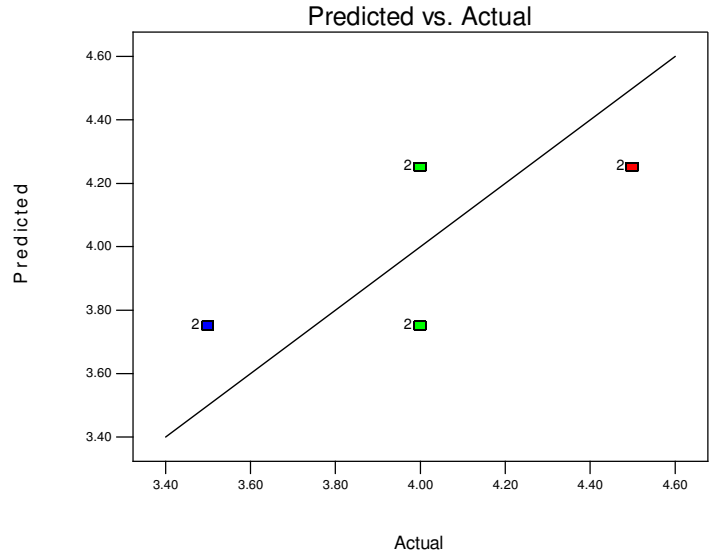
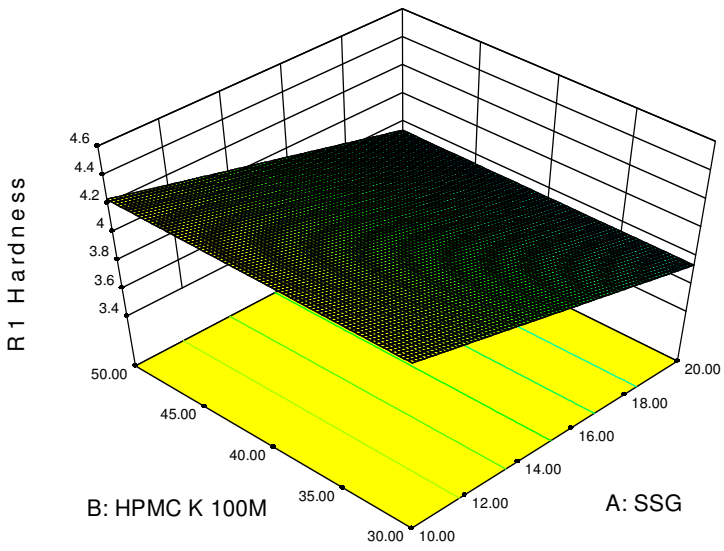


Figure 5.4.1.1(b): 3-D graph showing effect of SSG, HPMC K 100M on (R1) Hardness



Response: R2 (Drug release after 1hr)

Table 5.4.1.2(a) : ANOVA for factorial model

Source	Sum of Squares	DF	Mean Square	F Value	Prob >F
Model	**25.45**	**3**	**8.48**	**0.57**	**0.6635**
SSG	3.99	1	3.99	0.27	0.6317
Hpmc k 100m	1.52	1	1.52	0.10	0.7650
Eudragit RSPO	19.94	1	19.94	1.34	0.3112
Residual	59.46	4	14.87	-	-
Cor Total	84.91	7	-	-	-

Table 5.4.1.2(b): Estimated Regression Coefficients

Factor	Coefficient Estimate	DF
Intercept	7.49	1
A-SSG	0.71	1
B- HPMC K 100M	-0.44	1
C-Eudragit RSPO	1.58	1

Final Equation in Terms of Coded Factors:

R2 =Drug release after 1hr = +7.49+0.71 * A-0.44 * B+1.58 * C

Figure 5.4.1.2(a): Correlation between actual and predicted values for Hardness (R2)

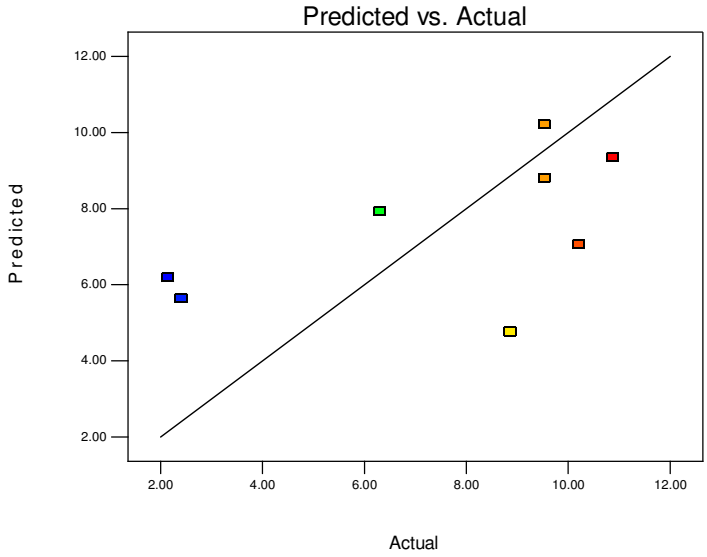
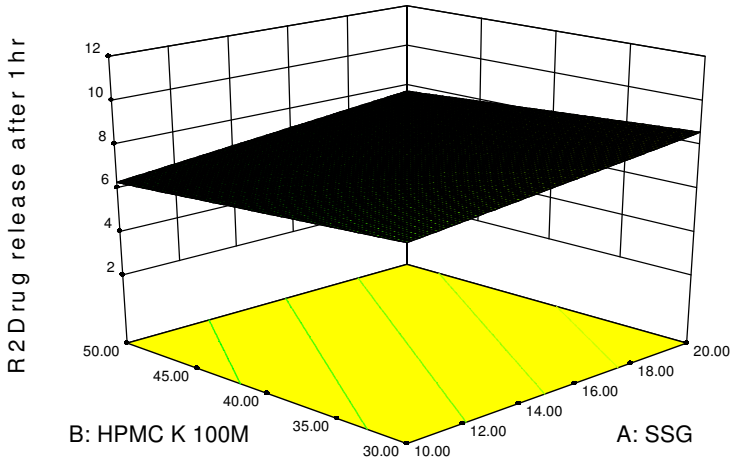


Figure 5.4.1.2(b): 3-D graph showing effect of SSG,HPMC K 100M on Drug release after 1hr (R2)



Response: R3 (Drug release 8hr)

Table 5.4.1.3(a): ANOVA for factorial model

Source	Sum of Squares	DF	Mean Square	F Value	Prob >F
Model	**196.52**	**1**	**196.52**	**6.95**	**0.0387**
C-Eudragit RSPO	196.52	1	196.52	6.95	0.0387
Residual	169.55	6	28.26	-	-
Cor Total	366.06	7	-	-	-

Table 5.4.1.3(b): Estimated Regression Coefficients

Factor	Coefficient Estimate	DF
Intercept	49.37	1
C-Eudragit RSPO	-4.96	1

Final Equation in Terms of Coded Factors:

R3 = R3 Drug release 8hr = +49.37- 4.96 * C

Figure 5.4.1.3(a): Correlation between actual and predicted values for Drug release 8hr (R3)

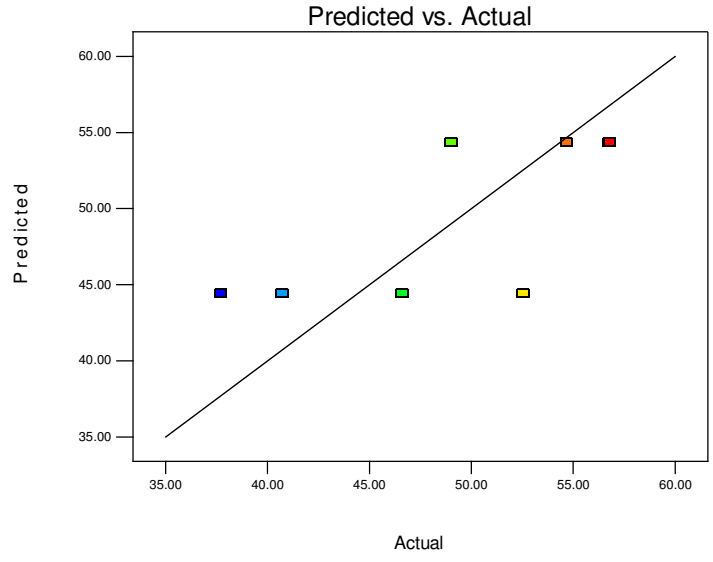
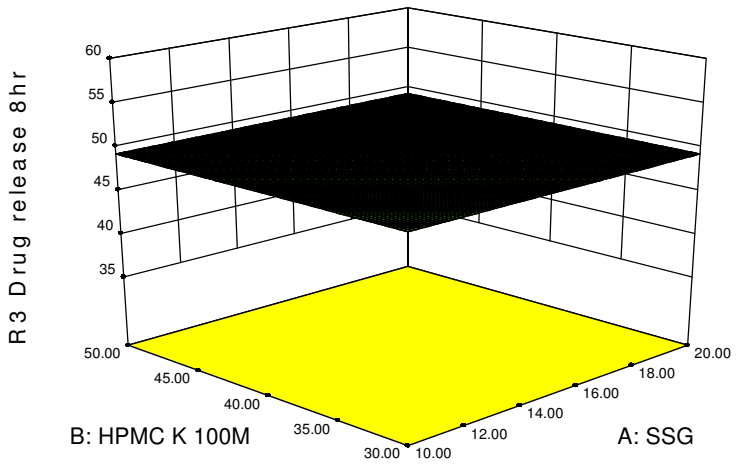


Figure 5.4.1.3(b): 3-D graph showing effect of SSG, Hpmc K100 M on Drug release 8hr (R3)



Response: R4 (Drug release 12 hr)

Table 5.4.1.4(a): ANOVA for factorial model

Source	Sum of Squares	DF	Mean Square	F Value	Prob >F
Model	**385.39**	**2**	**192.70**	**7.27**	**0.0331**
A-SSG	0.64	1	0.64	0.024	0.8828
C-Eudragit RSPO	384.75	1	384.75	14.51	0.0125
Residual	132.58	5	26.52	-	-
Cor Total	517.98	7	-	-	-

Table 5.4.1.4(b): Estimated Regression Coefficients

Factor	Coefficient Estimate	DF
Intercept	79.15	1
A-SSG	-0.28	1
C- Eudragit RSPO	-6.94	1

Final Equation in Terms of Coded Factors:

R4 = R4 Drug release 12hr = +79.15 -0.28 * A -6.94 * C

Figure 5.4.1.4(a): Correlation between actual and predicted values for Drug release 12hr (R4)

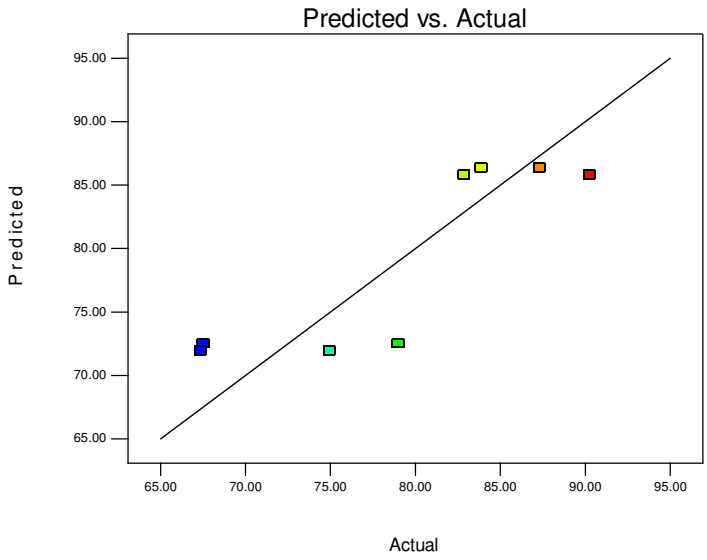
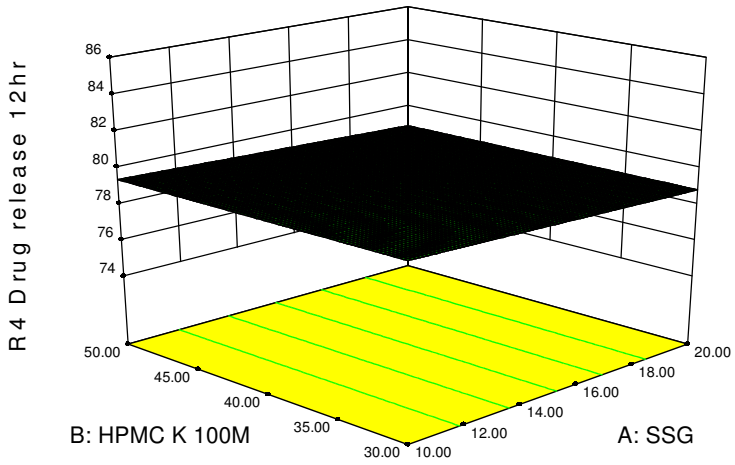


Figure 5.4.1.4(b): 3-D graph showing effect of SSG, HPMC K100 M on Drug release 12hr (R4)



Response: R5 (Friability)

Table 5.4.1.4(a): ANOVA for factorial model

Source	Sum of Squares	DF	Mean Square	F Value	Prob >F
Model	**0.015**	**6**	**2.529**	**22.48**	**0.1601**
A-SSG	2.813	1	2.813	25	0.1257
B-HPMC K 100M	5.513	1	5.513	49	0.0903
C-Eudragit RSPO	3.125	1	3.125	2.78	0.3440
RESIDUAL	1.125	1	1.125	-	-
Cor Total	0.015	7	-	-	-

Table 5.4.1.4(b): Estimated Regression Coefficients

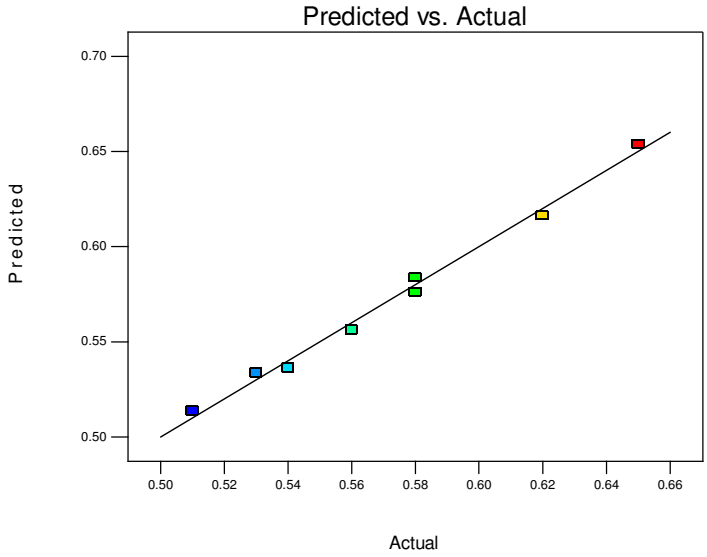
Factor	Coefficient Estimate	DF
Intercept	0.57	1
A-SSG	0.019	1
B-HPMC K 100M	0.026	1
C- Eudragit RSPO	-6.250	1

Final Equation in Terms of Coded Factors:

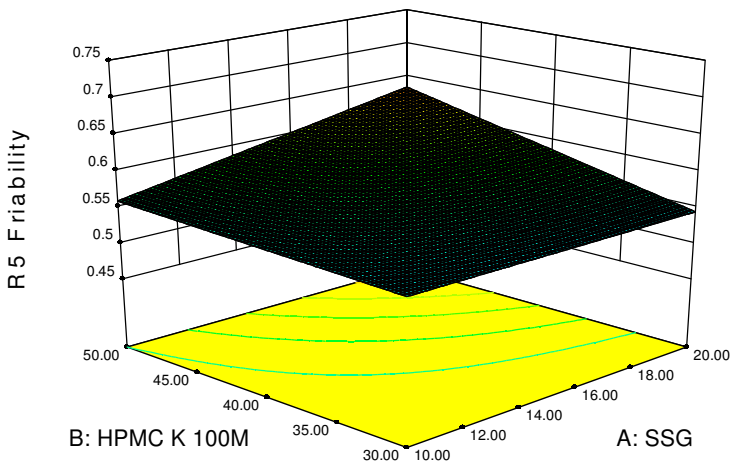
R5 = Friability =

+0.97500
-0.028250 * SSG
-4.50000E-003 * HPMC K 100M
-8.50000E-003 * Eudragit RSPO
+3.75000E-004 * SSG * HPMC K 100M
+4.25000E-004 * SSG * Eudragit RSPO
+3.75000E-005 * HPMC K 100M * Eudragit RSPO

Correlation between actual and predicted values for Friability(R5)



3-D graph showing effect of SSG, HPMC K100 M on Friability (R5)



Response: R6 (n value)

(a): **ANOVA for factorial model**

Source	Sum of Squares	DF	Mean Square	F Value	Prob >F
Model	**0.43**	**2**	**0.21**	**2.61**	**0.1678**
A-SSG	0.012	1	0.012	0.15	0.7162
C-Eudragit RSPO	0.42	1	0.42	5.06	0.0743
RESIDUAL	0.41	5	0.082	-	-
Cor Total	0.84	7	-	-	-

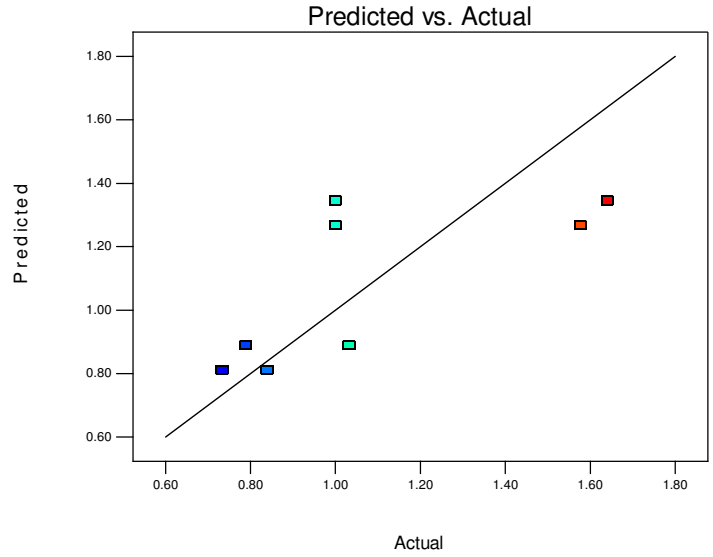
(b): Estimated Regression Coefficients

Factor	Coefficient Estimate	DF
Intercept	1.08	1
A-SSG	-0.039	1
C- Eudragit RSPO	-0.23	1

Final Equation in Terms of Coded Factors:

R6 n value = +1.08 -0.039 * A-0.23 * C

Correlation between actual and predicted values for n-value(R6)



3-D graph showing effect of SSG, HPMC K100 M on n-value (R6)

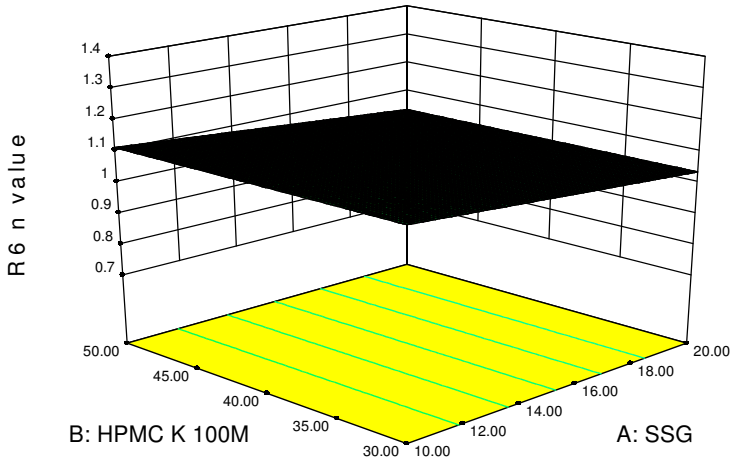


TABLE 5.4.1.5 Composition of the optimized formula.

*INGREDIENTS	R
LOSARTAN POTASSIUM	100
Sodium Starch Glycolate	20
HPMC K100M	30

EUDRAGIT RSPO	35.87
Magnesium Stearate	5
Talc	5
TOTAL	**195.87**

*All the quantities expressed are in mg / tablet.

TABLE 5.4.1.6 Comparison between the experimental (E) and predicted (P) values for the most probable optimal formulation

Optimized Formulation	Dependable Variables					
	Friability (%)	Hardness (kg/cm^2)	Drug release at 1 hr	Drug release at 8 hr	Drug release at 12 hr	n-value
Predicted	0.37	5.4	7.97	51.41	81.73	1.132
Experiment	0.33	5.0	10.30	60.35	89.10	0.924

Optimal formula												
TIME	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
%CDR	10.30	19.05	24.92	29.03	34.42	39.04	49.31	60.35	72.57	78.16	83.40	89.10

Sr. No.	**Parameters**	**Results**
1.	**Appearance**	**Good**
2.	**Hardness**	**5.0kg/cm²**
3.	**Friability**	**0.33%**
4.	**Drug content**	**99.52 %**

7.	**% Swelling index at 12 h**	**83.83%**
8.	**In- vitro drug release**	**89.10**

5.4.2 Stability studies

Table 5.4.2: At ambient condition (25±2°C and relative humidity 60± 5%)

Time	**Hardness (Kg/cm^2)**	**Friability (%)**	**Drug content (%)**	**Cumulative % drug released at 12 hr**
Initial	6.3±0.25	0.25	98.69±0.69	89.10
First Month	6.3±0.23	0.25	98.53±0.84	89.10
Second Month	6.3±0.32	0.27	98.58±0.57	89.10
Third Month	6.3±0.30	0.29	98.63±0.57	89.10

At elevated temperature (40±2°C and relative humidity 75± 5%)

Time	**Hardness (Kg/cm^2)**	**Friability (%)**	**Drug content (%)**	**Cumulative % drug released at 12 hr**
Initial	6.3±0.25	0.25	98.69±0.69	89.10
First Month	6.3±0.23	0.25	98.53±0.84	89.10
Second Month	6.3±0.32	0.27	98.58±0.57	89.10
Third Month	6.3±0.30	0.29	98.63±0.57	89.08

CHAPTER

6

DISCUSSION

6. DISCUSSION

Bilayer tablets are novel drug delivery system were combination of single or two drugs used as a single unit having bimodal release profile to improve patient compliance, for the better management of multiple complications. In the present study bilayer tablet immediate and sustained release of losartan potassium were prepared with an objective of improving patient compliance by effective management of hypertension.

The bilayer tablets were prepared by compressing losartan potassium as fast dissolving layer and sustained releasing layer.

Identification:

The losartan potassium was estimated using buffer solution(1.2,6.8 and 7.4 pH) and the calibration curve was constructed in this solution at 234 nm as shown in Table-5 and fig-6. The method obeys Beer-Lambert's law in the studied range of 4-20 mcg/ml with high ‗r' value of >0.996 and low SD value suggested that method was reproducible and hence suitable for estimation of losartan potassium.

Losartan potassium was formulated as fast dissolving layer using sodium starch glycolate as superdisintegrants in different concentration. And it prepared as sustained release layer using matrix forming material like HPMC, and eudragit rspo in different combination.

FTIR Study:

IR (KBr) cm^{-1} of pure drug losartan potassium exhibited characteristics absorption bands in the IR region as mentioned below:

The peak at 3227.0 due to hydrogen bonding caused by –NH & -OH groups. The peak at 3077 due to aromatic -CH stretching. The group of peaks between 2956 to 2671 may be due to –CH-H stretching of $–CH_3$ and $–CH_2$ groups.1575 may be due to –C=N stretching. 1575, 1472 may be due to C=C ring stretching 1423 may be due to -CN stretching, 1422 & 1340 may be due to –CH bending, 1260 & 1188 may be due to –OH & -CO bending, 844 may be due to 1, 4 – di-substituted phenyl ring, 754 may be due to substituted phenyl ring, 565 may be due to –C-Cl.

The IR data of the formulation was compared with the standard spectrum of pure drug losartan potassium and the characteristic peaks associated with specific functional groups and bonds of the molecule and their presence/absence in the polymeric carrier (formulation) were noted. The IR spectrum of the formulation showed that there is no significant evidence for interaction between drug and the polymer. Peaks of both drug as well as formulation were observed and interpreted. So this clearly suggest that the drug has not undergone any interaction with the polymer in the formulation, as there is no any shift in the positions of the characteristic absorption bands of drug in the formulation.

DSC study:

Micromeritic properties:

In the present study, direct compression method was adopted for IR layer. Hence the mixture of drug and ssg should posses good flow and compaction properties. Plain losartan potassium exhibited angle of repose value of 41.22 ± 0.16° indicating poor flow property. It was furthersupported by high Carr's index (31.19 ± 0.14) and Hausner's ratio (1.45 ± 0.07). Hence lubricants were added to improve the flow property of drug. The angle of repose of all the blend was within range of 27.58 to 31.21° indicated excellent flow property of powder blend.

Non aqeous wet granulation method was adopted for SR layer. Hence the mixture of drug and polymer should posses good flow and compaction properties. Plain losartan potassium exhibited angle of repose value of 37.22 ± 0.16° indicating poor flow property. It was further supported by high Carr's index (36.19 ± 0.14) and Hausner's ratio (1.38 ± 0.07). Hence lubricants were added to improve the flow property of drug. The angle of repose of all the blend was within range of 26.04 to 30.06° indicated excellent flow property of powder blend.

Physico-chemical evaluation of tablets:

The results of physico-chemical evaluation of bilayer matrix tablets are given in Table 7 & 8. The tablets of different batches of hpmc, eudragit rspo and SSG in combination were found uniform with respect to thickness (3.46. to 3.64 mm). Hardness (6.1 to 6.5 kg/cm^2) and friability (0.21 to 0.41 %) were also found uniform indicating good handling property of the prepared bilayer matrix tablets. Weight variation (1.2 to 2.1 %) and drug content (97.5 to 99.9%) were within prescribed limits. Hence tablets containing drug, polymer, binder and lubricants could be prepared satisfactorily by direct compression and non aqeous wet granulation method.

Swelling study:

Investigation of polymer swelling and erosion is a valuable exercise to better understand the mechanism of release and the relative importance of participating parameters. Bilayer matrix tablets of HPMC K 100M, Eudragit Rspo and SSG was not found intact throughout the period of swelling in phosphate buffer of pH 6.8. The swelling index of matrix tablets were directly proportional to the concentration of the polymer, as the polymer concentration increases there was increase in the swelling index. After 7 or 8hrs there was decrease in swelling index due to the erosion of surface layer of matrix tablet. Formulation (f2 to f7) showed better swelling index up to 7 hr then it starts to decline. the formulation (f1&f8) showed better swelling index up to 8 hr then it starts to decline. On comparing the swelling index, it was observed that f6 & f7 swell more compare to other formulation. Table 9 &10 and Fig 14-16 depicts the swelling behavior of different matrix tablets. The order of swelling of polymeric tablets were f1>f4>f8>f2>f3>f5>f6>f7.

***In-vitro* release study:**

A hydrophilic and hydrophobic matrix controlled release system is a dynamic system composed of polymer-wetting, hydration and dissolution. At the same time, other soluble excipients or drug(s) will also wet, dissolve and diffuse while the insoluble ingredients will be held in place until the polymer erodes or dissolves. Since the diffusional release of soluble drug such as losartan potassium may primarily be controlled by the gel thickness (diffusion layer), increasing polymer level tends to decrease drug release. The most common explanation of the effect of increase in the polymer level on drug release is that, it results in the increase in the thickness of the gel layer, which retards drug diffusion out of tablet. Given the complexity of these swellable

matrix systems other factors such as, differences in water penetration rate, water absorption capacity and swelling, polymer erosion and attrition which result from changes in the polymer content may contribute to this effect.

Dissolution studies of prepared bilayer matrix tablets were carried out in pH 1.2 for first 3 hours , pH 6.8 for 4 hour and pH 7.4 for 4 hour. The samples were analyzed spectrophotometrically at 234 nm.

Effect of sodium starch glycolate:

Presence of super disintegrant (sodium starch glycolate) in Immediate release layer showed faster disintegrant of the layer. This can attributed to the extent of water uptake and consequently the strong swelling power of this disintegrant causing sufficient hydrodynamic pressure to induce complete disintegration. The concentration of ssg is directly propotional to release of drug. Pattern was shown in Table 11.

Effect of HPMC K100M:

The release pattern of HPMC K100M bilayer matrix tablet made with polymer concentration of 14.7 – 19.76 % w/w were shown in Table 16-17 . It indicated that the drug release was spread over extended period of 12 hrs with the variation of the polymer level. The dissolution rates from formulation f3 (HPMC 19.76% w/w), f5 (HPMC 14.7%w/w) were 67.54 and 94.82% in 12 hrs . It was evident the as the polymer level increases the percent of drug release decreases resulting controlled release. As the proportion of HPMC K100M was increased there was a progressive decline in the release

rate because of the polymer gel formed was more likely to be resistance to drug diffusion and gel erosion. The observation was in accordance with our swelling study of HPMC K100M showed that increase in the swelling index with polymer level.

Effect of EUDRAGIT RSPO:

The release pattern of EUDRAGIT RSPO bilayer matrix tablet made with polymer concentration of 14.7 – 19.76 % w/w were shown in Table 16-17 . It indicated that the drug release was spread over extended period of 12 hrs with the variation of the polymer level. The dissolution rates from formulation f3 (EUDRAGIT RSPO 19.76% w/w), f5 (EUDRAGIT RSPO 14.7%w/w) were 67.54 and 94.82% in 12 hrs . It was evident the as the polymer level increases the percent of drug release decreases resulting controlled release. As the proportion of EUDRAGIT RSPO was increased there was a progressive decline in the release rate because of the polymer gel formed was more likely to be resistance to drug diffusion and gel erosion. The release of drug from matrix tablets depends not only on the nature of the polymer but also drug polymer ratio.

Mechanism of drug release:

To study the release mechanism of bilayer matrix tablets, various dissolution models were applied to the *in-vitro* release profiles of different formulations. The kinetic models included zero order, first order, Higuchi and Korysmeyer-Peppas equations. As observed from the Table 28 & 29 the values of correlation-coefficient (r^2) for all the formulations were high enough to evaluate the drug dissolution behavior by equation.

The value of release exponent (n) was found to be a function of polymer used and the physicochemical property of a drug molecule itself. Kinetic results revealed that, the formulations f2 & f3 followed first order kinetics as correlation coefficient (r^2) values (0.981-0.975) are higher than that of zero order release kinetics and f1,f3,f4,f5,f6,f7,f8 formulations followed zero order rlease kinetic. The prepared hydrophilic bilayer matrix formulations(F1,F2,F5,F6,F8) showed Non-Fickian (anomalous) case-11 trasport release, as the values of release exponent (n) lies between (1.001-1.641) with their correlation coefficient (r^2) values between 0.968-0.995, indicating that diffusion, polymer swelling and erosin were involved in the release process. The formulations(F3,F4,F7) showed Non-Fickian (anomalous) trasport release, as the values of release exponent (n) lies between (0.734-0.840) with their correlation coefficient (r^2) values between 0.958-0.983, indicating that diffusion, polymer swelling were involved in the release process

Discussion for Optimization

Effect of formulation variables on Hardness

The hardness for formulations was varied from 6.1kg/cm^2 to 6.5kg/ cm^2 table no.

The constant and regression co efficient for R_1 = + 4.00 - 0.25 * A

In this case there is significant terms.

The linear Model for R_1 was found to be Significant for hardness. The model F-value of 6.00 and the value of p is 0.0498 indicate the model is significant. From response surface plot it was obtained that, when the concentration of SSG increase there is decrease in hardness, as decrease in the concentration of ssg increase in hardness.

Effect of formulation variables on Invitro drug release 1hr.

The Invitro drug release 1hr for formulations was varied from 9.005% - 18.14%.

The constant and regression co-efficient for R_3=+7.49+0.71*A -0.44* B+1.58*C In this case there are no significant model terms.

The linear Model for R_2 was found to be not Significant for Invitro drug release 1hr. The model F-value of 0.057 and the value of p is 0.6635 indicate the model is not significant.

The factor A has positive effect which indicates that Invitro drug release 1hr increases as factor (SSG) increases. The factor B has negative effect which indicates that Invitro drug release 1hr increases as factor (HPMC K100M) decreases. The factor C has positive effect which indicates that Invitro drug release 1hr increases as factor (EUDRAGIT RSPO) increases.

From response surface plot it was obtained that, when the concentration of HPMC K 100M was kept at low level and concentration of SSG was increased simultaneously there is change in In vitro drug release 1hr.

Effect of formulation variables on Invitro drug release 8hr.

The Invitro drug release 8 hr for formulations was varied from 40.73% to 63.69%

The constant and regression co-efficient for R_4=+49.37 - 4.96 * C

In this case C is significant model term.

The linear Model for R_3 was found to be Significant for Invitro drug release 8hr. The model F-value of 6.95 and the value of p is 0.0387 indicate the model is significant.

The factor C has negative effect which indicates that In vitro drug release 8hr decreases as factor (EUDRAGIT RSPO) increases. From response surface plot it was obtained that, when the concentration of HPMC K 100M was kept at low level and concentration of SSG was increased simultaneously there is increase in Invitro drug release 8hr.

Effect of formulation variables on Invitro drug release 12hr.

The Invitro drug release 12hr for formulations was varied from 67.54% to 94.82%.

The constant and regression co-efficient for R_4=+79.15 -0.28 *A -6.94 * C

In this case A , C are significant model terms.

The linear Model for R_4 was found to be Significant for In vitro drug release 12hr. The model F-value of 7.27 and the value of p is 0.0331 indicate the model is significant.

The factor A has negative effect which indicates that In vitro drug release 12hr decreases as factor (HPMC K 15M) increases. The factor C has negative effect which indicates that Invitro drug release 12hr increases as factor (EUDRAGIT RSPO) decreases. From response surface plot it was obtained that, when the concentration of HPMC K 100M was kept at low level and concentration of SSG was increased simultaneously there is increase in In vitro drug release 12hr.

Effect of formulation variables on Friability

The friability for formulations was varied from 0.21% to 0.41% table no.

The constant and regression co efficient for R_2 = +7.49 +0.71* A -0.44* B +1.58 * C

In this case A, B and BC are not significant terms.

The linear Model for R_5 was found to be not Significant for Friability. The model F-value of 0.57 and the value of p is 0.6635 indicate the model is not significant. The factor A has positive effect which indicates that friability increase as factor (SSG) increases. The factor B has negative effect which indicates that friability increases as factor (HPMC K100M) decreases. The factor c has positive effect which indicates that friability increases as factor (Eudragit Rspo) increases.From response surface plot it was obtained that, when the concentration of HPMC K 100M was kept at low level and concentration of SSG was increased simultaneously there is steep increase in friability.

Effect of formulation variables on N value.

The N value for formulations was varied from 0.734 to 1.641.

The constant and regression co-efficient for R_6=+1.08 -0.039 * A-0.23 * C
In this case there are no significant model terms.

The linear Model for R_6 was found to be not significant for N value. The model F-value of 2.61 and the value of p is 0.1678 indicate the model is not significant.

The factor A has negative effect which indicates that N value increases as factor (HPMC K 100M) decreases. The factor C has negative effect which indicates that N value increases as factor (EUDRAGIT RSPO) decreases.

From response surface plot it was obtained that, when the concentration of HPMC K 100M was kept at low level and concentration of SSG was increased simultaneously there is increase in N value. In the same case, when the concentration of SSG was kept at

low level and concentration of HPMC K 100M increased simultaneously there is decrease in N value.

Stability studies:

The stability studies were carried out for the optimized formula at 40±2°C/ 75±%5 RH for one month. Table 20 shows the values of post-compressional parameters after stability studies at different temperature and humidity conditions. The results indicated that the tablets did not show any physical changes (hardness and friability) during the study period and the drug content was found above 98% at the end of one month. This indicates that tablets are fairly stable at storage condition.

CHAPTER

7

CONCLUSION

CONCLUSION

The following conclusions can be drawn from the results obtained.

- Preformualtion studies on losartan potassium corroborate with the reported literature limits.
- The adopted method yielded uniform and reproducible bilayer matrix tablets with all the polymers used.
- The hardness, friability, weight variation, drug content, swelling index and *in vitro* release were uniform and reproducible.
- The swelling index of HPMC K100M bilayer matrix tablets was studied among the formulation.
- The release was inversely proportional to the polymer concentration irrespective of the polymer used.
- The release profile of bilayer matrix tablets containing 13.27% w/w of Hpmc K100m And Eudragit Rspo (F5) which has given 94.82% release .
- The release rate of bilayer matrix tablets containing 19.47% w/w of Hpmc K100m And Eudragit Rspo (F3) which has given 67.54% release. Hence as the polymer ratio increase drug release will decline.
- The mechanism of drug release was found to be non-fickian case-11 trasport.
- Selected bilayer matrix tablets were found to be stable with respect to drug content, friability, weight variation, hardness and thickness.
- FTIR and DSC studies revealed no chemical interaction and indicating stability of drug in tablets.

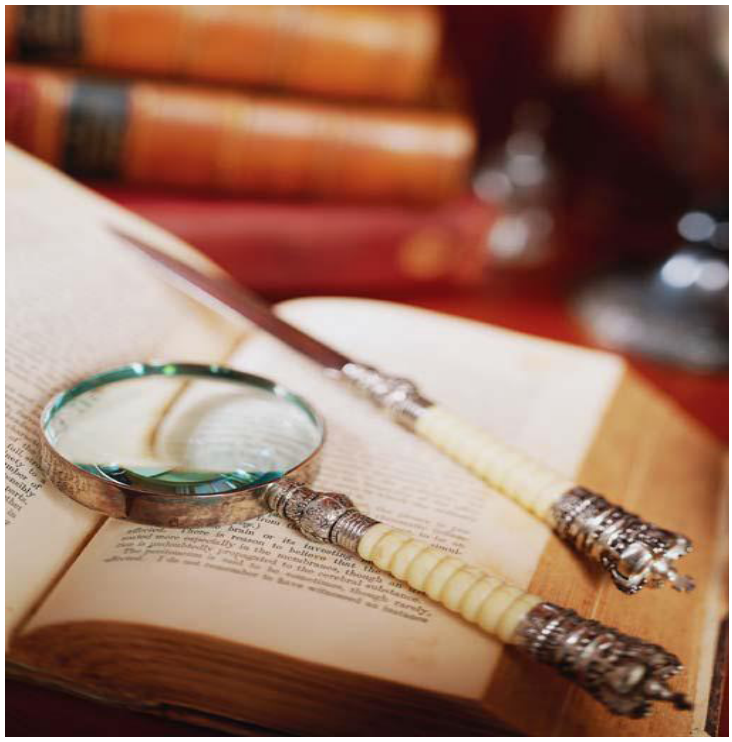
- Hence, bilayer matrix tablets containing Hpmc k 100m, Eudragit rspo, Ssg (f5) of losartan potassium showed promising results.

- Optimized formulation exhibited in-vitro drug release rate as per USP.

CHAPTER

8

SUMMARY



8. SUMMARY

The use of hydrophilic matrices has become extremely popular in controlling the release rate of drugs from solid dosage forms. These systems are attractive from an economic as well as process development view point.

Losartan potassium, an oral antihypertensive agent used in the treatment of hypertension. The short biological half-life (about 2 - 2.5 hrs) and frequency of administration makes losartan potassium an ideal candidate for oral controlled release.

Chapter 1 deals with introduction on oral drug delivery system, combination therapy for treatment of multiple diseases, Potential Reason for Considering the Double-layer Dosage Form, Some novel bilayer and trilayer tablet devices**,** Bilayer problems , Bi-Layer tablets: Quality and GMP-requirement, Sustained Release Drug Delivery Systems.

The objective of the study was to formulate and evaluate bilayer matrix tablets of losartan potassium employing Ssg ,Eudragit Rspo and Hpmc K100m as stated in chapter 2.

A detailed review of literature on bilayer matrix formulations and evaluations of pure drug losartan potassium, excipients like sodium starch glycolate, Eudragit Rspo and Hpmc K100 was collected by referring different journals, books and is presented in chapter 3.

Methodology used in the preformulation of losartan potassium, formulation and evaluation of bilayer matrix tablets is described in chapter 4. Drug, polymers and reagents were procured from different sources. Methodology on formulation and evaluation of bilayer matrix tablets was adopted from reported methods. Formulation

variables include nature and concentration of polymers, and their combinations. Bilayer matrix tablets are characterized for physico-chemical properties, in vitro release and stability. Experiments were conducted in triplicate.

Chapter 5 contains the results obtained from formulation and evaluation of bilayer matrix tablets and the data are presented in Tables and Figures. The discussion on results obtained during the present study is given in chapter 6.

Preformulation studies on losartan potassium were in agreement with reported literature. The method adopted in the preparation yielded tablets with uniform weight, thickness, hardness; friability and drug content was found within the prescribed limits. Modulation of drug release was effected by nature and concentration of polymers. The swelling index of Hpmc k 100m, Eudragit rspo bilayer matrix tablets was compared with other formulation(f1-f8). Among all the formulations, f5 were given complete and sustained drug release over a period of 12 hrs.

All these9(f1-f8) bilayer matrix tablets exhibited non-fickianan (anomalous) and Non-Fickian case-II trasport diffusion. Among all these formulations f5 was selected as best formulation because polymer in low concentration, which showed better sustained drug release over12 hr, as compared to other selected formulation. Bilayer matrix tablets were found to be stable with respect to drug content, friability, hardness and weight variation during the stability study period. FT-IR and DSC study revealed no interaction between drug and excipients used.

Conclusion was drawn from the discussion and placed in chapter 7. The present study conclusively proved that controlled release bilayer matrix tablets of losartan potassium can be efficiently prepared by using HPMC K100M,eudragit rspo and ssg their combinations. And the prepared tablets gave the promising results for once a day administration of losartan potassium.

Vancouver style was followed to write the references quoted in the study and is listed in the chapter of bibliography

CHAPTER

9

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9. BIBILOGRAPHY

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